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THE SIGNIFICANCE OF PATTERN RECOGNITION RECEPTORS IN THE PATHOGENESIS OF SOME DISEASES

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Abstract. This review article discusses the basic concepts of membrane-bound receptors of innate immunity – Toll-like receptors. Basic methods for the determination of their expression used in clinical studies, as well as the results obtained with them are discussed. Prospects for future research based on complete information about the system TLR also discussed. These studies will clarify the molecular defects and localize disturbances in the innate immune system and will evaluate their role in the pathogenesis and treatment of a wide range of diseases.

Individual susceptibility to infection is determined by pathogens, environmental factors and the state of the immune system [1]. Protection at the local level after contamination is carried out by typical inflammatory response, which aims to recognize and destroy the pathogen and its components. B and T lymphocytes carrying the adaptive immune response recognize pathogens using high-affinity receptors. However, the development of adaptive immunity typically is slow enough, as it assumes the activation, proliferation of lymphocytes and synthesis of proteins, such as cytokines and immunoglobulins. A more rapid development of immune reactions is provided by the innate immune response which recognizes the pathogens with special receptors that have broader specificity than the lymphocyte receptors [2].

The mechanisms by which the innate immune system recognizes pathogens are sufficiently evolutionarily stable and provide effective protection of the organism, despite the rapid mutational variability in viruses and bacteria. The main reason for the continued effectiveness of this is that the innate immune system by soluble and cell-bound receptors recognizes the broad structural patterns. They are rather conservative groups within certain pathogens and are usually necessary for survival, and usually are absent in the host. Recognition is performed by two types of so called pattern-recognition receptors: cellular and soluble. Mannose-binding lectin receptors, immunoglobulin receptors, proteins of the complement system, scavenger receptors, and some others are cellular receptors [3,4].

These receptors are called pattern recognition receptors (PRR), as they recognize specific molecular patterns. The corresponding molecular structures that are composed of pathogens are called pathogen-associated molecular patterns (PAMS). PAMS recognize PRR with different chemical nature, including specific combinations of sugars, some proteins, lipid-containing molecules, and nucleic acids, some patterns. Limitation of recognition of the innate immune system by molecular structures included in the composition mainly bacteria, viruses and other pathogens aims the innate immune system primarily to infectious and not on any objects foreign to an organism. For example, double-stranded RNA is an intermediate product required for replication of RNA viruses, and its recognition is an important trigger innate anti-viral protection. Detection of Gram-negative bacteria is accomplished by recognition of the LPS component of the outer membrane. The presence of the LPS component is necessary for the survival of the majority of this type of bacteria. Recognition of Gram-positive bacteria is carried out in contact with the receptors of innate immunity conservative PAMS, forming part of their cell walls. Such structures are peptidoglycan and lipoteichoic acid, which are necessary for the structural integrity of their cell walls [5, 6].

A special group of cellular receptors are the Toll-like receptor (TLR), which are located mainly on the surface of cells of innate immunity. These receptors are primarily detected PAMS bacteria, viruses and other pathogens, and play an important role in the development of the innate immune response.

These receptors recognize molecular structures that are common to whole groups of pathogens. TLR interact with molecular structures that do not exist in humans, but present on pathogens. TLR are widely distributed in the cells of host. They induce the activation and expression of specific genes whose expression controls mechanisms ensuring the destruction of invading pathogens. As a result of TLR activation a wide spectrum of biological responses appears inducing the synthesis of pro-inflammatory cytokines and interferons which implement innate immune responses as well as the expression of costimulatory molecules that facilitate activation of T-lymphocytes, and stimulate development of the adaptive immune response [5, 7].

The main stages of intracellular activation from TLR signaling to the cell nucleus. The first step is to generate a signal, i.e. ligand binding to the corresponding TLR. Formation of intracellular components of the induced signal and performing active signaling pathway occurs thereafter. The main elements of this ensemble are adapter proteins (such as MyD88 and TRIF). They specifically bind to the intracellular domain of TLR specific and intracellular proteins, they combine and provide the transmission signal to the cytoplasm. The so-called "second messenger" is formed inside the cell. They are molecules which can diffuse into other areas of cells and stimulate secondary changes there. Activation key enzymes ща signal transduction (protein kinases and protein phosphatases) is the next step. Kinases catalyze the phosphorylation of corresponding amino acid residues that are part of the protein (tyrosine, serine, threonine) involved in signal transduction. Phosphatases catalyze the dephosphorylation and cancel the effect of kinases. The subsequent multiplication of the signal carried out by means of a number of enzymes. Included in the signal transduction pathway enzymes (IRAK-kinases and MAP-kinases) catalyze many subsequent reaction after the initial activation. Then, they cause the formation of a large number of molecules of the next component, which considerably increases the signal at each stage of the transmission in the cytoplasm. As a result, a large number of effector molecules such as nuclear transcription factor NFκB and interferon regulatory factor IRF are formed. NFκB stimulates transcription of genes that control the synthesis of proinflammatory cytokines [6, 8, 9].

It was found that each type of TLR recognizes a well-defined repertoire of conservative molecular structures of pathogens. Full set of Toll-like receptors, those are present in human or mouse, can detect a plurality of different pathogens (viruses, bacteria, fungi, and even protozoa).

Currently ten TLR men ligands are identified. Most PAMS which are recognized by TLR are conserved molecular structures. They are necessary for the integrity, performance or replication of certain pathogens. For example, the viruses can't operate without their essential component - the nucleic acids. Gram-negative bacteria can't exist without the LPS-containing walls, and zymosan is necessary components of the cell walls of fungi. Mutations in pathogens that affect their basic structural components are usually lethal. Double-stranded RNA, which is a ligand for TLR3, is obligatory intermediate product in replication of RNA viruses. Therefore TLR3 very effectively detects contained in the cell cytoplasm RNA viruses.

There are associated with dangerous situations for the life of cells, molecular structure – DAMPs among the ligands that are recognized by TLR. Such structures are formed when damaged cells and tissues are in different stress conditions (thermal, chemical and mechanical) and in cell necrosis and apoptosis. Such ligands are, for example, heat shock proteins (HSP60, HSP70), low density lipoproteins, cells associated with chromatin protein HMG-B1, which is released upon cell necrosis, and others. Excessive activation via TLR innate immune cells may lead to the development of a number of pathological inflammatory processes in the body. These include local and systemic autoimmune processes, the formation of large pockets of necrotic tissue in stroke and heart attack, with massive burns, injuries and severe infections, including sepsis. Ligands that are recognized by TLR are highly diverse in chemical nature. These include proteins, lipids, polysaccharides and nucleic acids. Some TLR directly bind to their ligands. But in other cases, the recognition process also involves accessory proteins. An example of such recognition is the binding of bacterial LPS to TLR4, which contribute two auxiliary MD-2 protein and lipid soluble binding protein.

Monomers LPS are extracted from bacterial membranes using serum lipid binding protein. Lipid-binding protein carries monomer LPS to a lipid-binding protein portion of the molecule on the membrane of the phagocyte SD14. CD14 promotes the binding of LPS to the complex TLR4 - MD-2. Interaction with LPS complex TLR4 - MD-2 leads to the transfer of the signal inside the cell TLR4. It was experimentally demonstrated that genetic deletion of the protein CD14 on the surface of neutrophils and macrophages or blocking its functions via monoclonal antibodies significantly reduce the sensitivity of these cells to bacterial LPS [6,10].

Toll-like receptors that interact with extracellular ligands are included in the plasma membrane of the host cell. TLR, that bind ligands which are formed within the cell are associated with intracellular membranes. For example, TLR, which recognize components of the cell walls of bacteria and fungi (TLR2, TLR4, TLR5, TLR6), are located on the surface of cells of innate immunity. At the same time, TLR, which recognize viral or microbial nucleic acid (TLR3, TLR7, TLR8, TLR9), are localized to intracellular membranes. They contact with their ligands in phagolysosomes or endosomes. Such localization of these receptors enables detecting nucleic acids released from microbial cells or virions after phagocytosis and their partial hydrolysis.

Certain TLR form dimers, including other TLR. For example, TLR4 forms homodimers, TLR2 can form heterodimers with TLR1 and TLR6. Formation of dimeric complexes affects their specificity. Formation of dimeric complexes affects their specificity. This allows such a receptor recognize LPS, zymosan, lipoteichoic acid, peptidoglycan of bacteria and bacterial lipoproteins. TLR2 + TLR1 heterodimers recognize bacterial lipoproteins and some characteristic surface proteins of the parasite.

TLR5 recognizes flagellin monomers (the main structural component of bacterial flagella) and monomers TLR3 recognizes double-stranded RNA, which appears in the cytoplasm of cells after infection with RNA viruses. Single- RNA of viruses is a ligand for monomeric receptors TLR8 and TLR7. Monomer TLR9 recognizes and initiates a response against CpG DNA sequences, which are characteristic of microbial DNA and practically do not occur in vertebrate DNA [6,9,11]. TLR are widely distributed in the cells of microorganism. It was established that TLR are expressed on most cells in the mammalian body. However, for the induction and development of both innate and adaptive immune responses TLR play a most important roleThey are presented in monocytes / macrophages, dendritic cells, neutrophils, mast cells, NK-cells, mucosal epithelium. These cells constitute the first barrier to the penetration of pathogens into the body, as well as vascular endothelial cells. The main cell types of the innate and adaptive immune systems expressing different TLR number are shown in Table.

Expression of TLR cells of the innate and adaptive immunity

Cell types	TLR									
	1	2	3	4	5	6	7	8	9	10
Monocytes/ Macrophages	+	+	–	+	+	+	–	+	+	–
Dendritic cells	+	+	+	+	+	–	+	–	+	+
Neutrophils	+	+	–	+	–	–	–	–	+	–
Mast cells	+	+	+	+	–	+	–	–	+	–
NK-cells	+	–	+	–	+	+	–	+	–	–
Mucosal epithelial cells and vascular endothelial	+	+	–	+	+	–	–	–	–	–
B lymphocytes	+	–	–	–	–	++	+	–	+	+
T lymphocytes	+	–	–	–	+	–	–	+	–	–

A wide range of TLR ligands and the representation of these receptors on many cells promote the involvement of TLR in the pathogenesis of many diseases. Defects in the TLR can lead to development of serious infectious diseases (sepsis, meningitis), autoimmune diseases, atherosclerosis, allergy [12, 13]. Such defects include disorders recognition ligands, expression of TLR, signal transduction, production of effector molecules and gene polymorphism TLR. Defects molecules involved in signal transduction from the TLR are the basis increased susceptibility to infections. For example, children with a mutation in the gene encoding the IRAK-4 kinase, from an early age suffer from severe pyogenic infections caused by

Gram-positive organisms [14]. At the same time, excessive activation signaling pathway from the TLR is associated with development of sepsis, inflammatory bowel disease which can cause tissue destruction. The number of associations between the various pathologies and disorders in the TLR is growing. In connection with this, adequate and reliable methods of analysis of TLR are nesessary to identify immunodeficiency disorders associated with impaired functional activity of TLR that can be replicated in a standard clinical laboratory [15].

Determination of the expression of TLR. TLR expression on the cell surface is often determined by immunofluorescence. The principle of this method is that it uses fluorescent dyes labeled monoclonal antibodies (MABs) against CD - markers of cell types simultaneously with other fluorochrome-labeled MABs for the studied TLR (method of "double labels").

1. Flow cytometry laser.

Sample preparation for flow cytometry is usually carried out as follows: the nucleus containing cells in peripheral blood are being isolated from erythrocyte sedimentation with 3% gelatin solution. The cell suspension for the study of intracellular TLR expression is pretreated with fixing solution. Then the antibodies are being added. To study the expression of surface TLR processing with this solution is not required as TLR1, 2, 4, 6 and 10 are predominantly membrane associated. Treatment of secondary anti-mouse antibody labeled with PE or FITS must also conform to generally accepted standards. As isotype control of cytometric measurements IgG-fraction from the non-immunized mice is used. The final analytic concentration is 2x106 cells / ml. Flow cytometry is performed on a laser device with an argon laser with a wavelength of 488 nm. Cytograms study of cell suspension is derived on base of recorded parameters, the forward scattered light (FSC) and side light scatter (SSC) in the mode of dot-plot. Analysis of the fluorescence intensity and the percentage of fluorescent cells is carried out in the green region (FITS) FL1 (530 nm) and orange region (PE) FL2 (585 nm). Cells are analyzed in argon laser beams at a flow rate of 5000 cells / sec. Mean fluorescence intensity of cells is expressed in arbitrary units of fluorescence (AUF).

2. m-RNA expression of TLR genes.

m-RNA expression of TLR genes is usually determined by PCR in "real time" (RT), combined with reverse transcription by using specific primers. For example, expression of TLR2 and TLR4 gene can be carried out by using the following primers: a TLR-2 - TLR2-F1-CCTTCACTCAGGAGSAGCAAGC, TLR2-R1 - TGGAAACG-GTGGCACAGGAC; to the TLR-4 - TLR4TF6 - GAAGGGGT-GCCTCCATTTCAGC, TLR4-R6 - GCCTGAGCAGGGTCT-TSTSSA. TLR expression levels of mRNA are controlled by the gene GAPTAH (GAPDH-F1 - TGC-MTCCTGCACCACCAACT; GAPDH-F2 - YGCCTGCTTCAC-SASSTTS) due to the similar expression of this gene in human reproductive tract tissues [16].

Currently, methods using these studies were conducted in tens study of Toll-like receptor for various human diseases.

Some authors have conducted a comparative analysis of the expression of receptors TLR and NOD-2 in nasal polyps tissue and peripheral blood cells and the role of these parameters in the pathogenesis of polypoid rhinosinusitis was evaluated [17, 18].

As result of research TLR and NOD receptors, the researchers showed that the greatest pathogenetic significance lies in authentic increase in the expression of receptors TLR4 and TLR5 on granulocytes, monocytes and peripheral blood lymphocytes and cells of the inflammatory infiltrate in nasal polyps. Authentic inhibition of expression of TLR7 in these same cells is also shown. It is known that activation of innate immunity, TLR expression amplification entails a plurality of pathophysiological effects [8]. As for the pathogenesis of polypoid rhinosinusitis, where bacterial and fungal infection plays a role trigger immune inflammation in situ, the most important consequence is overproduction of pro-inflammatory cytokines and chemokines, which is a major factor in the formation of cellular inflammatory infiltrate. Intensification of phagocytic and antigen-presenting cell function macrophage-monocytic series, which is accompanied by overproduction of inflammatory mediators, is also characterized. As a consequence, the activation of the adaptive immune system for the deployment of the antigen specific lymphocyte immune response develops in situ [18–20].

Some authors [15] have developed an approach to the evaluation of system components TLR in healthy subjects, patients with immunopathology (common variable immune deficiency - CVID) and pathological processes in acute noninfectious origin (acute myocardial infarction - AMI). Functional activity of TLR was assessed by TNF-α production by human peripheral blood monocytes in response to

ligands of TLR. TNF-α is one of the main effector cytokines, providing for the development of the inflammatory response. In the proposed method, the authors used the mononuclear cells, but not whole blood, as the soluble inhibitors of TLR, cytokines, preexisting plasma may affect the assessment of the TLR negatively. Investigations have shown that the mononuclear cells of patients with CVID are characterized by low growth level of TNF-α in response to ligands TLR2, 6, 4 and 5 in vitro. This can lead to a weakening of immune function in these patients by repeated infection in vivo. With the development of acute pathological states such as myocardial infarction, an important role is played by the innate immune cells - neutrophils, macrophages and pro-inflammatory cytokines. Their expression can be induced in the cells by activation of innate immunity receptors. In the study of spontaneous and induced TLR ligands TNF-α production by mononuclear cells of patients with AMI, the authors showed that the predictor of adverse outcome of disease may be an additional increase in the production of TNF-α by mononuclear cells of patients in response to TLR ligands LPS and zymosan to 14th days after the development of myocardial infarction compared with induced expression of TNF-processing-α in the 1st day of the disease [15].

Some authors [16] examined the relationship mRNA levels of TLR2 and TLR4 with changes in immunoglobulin profile urogenital tract in women with chlamydia. The authors found an association immunoglobulin profile and mRNA expression of receptors of innate immunity cells of the cervical canal (CC) in the pathogenesis of urogenital chlamydiosis (Ugh). It is shown that the level of IgG, IgM, IgA, slgA, as well as the expression of TLR2 and TLR4 receptors characterize current of the infection process, the severity of clinical manifestations and outcome of the disease. Increased expression of TLR2 and TLR4 in combination with increased local synthesis slgA may contribute predominantly local inflammation and a favorable outcome of the disease. According to the researchers, these indicators can be used as additional criteria in the evaluation process of chlamydial forms and severity of its course. Other authors [21] investigated the role of Toll-like receptors in the development of immune inflammation in the skin of patients with psoriasis. Study of the amount and distribution of Toll-like receptor TLR2, TLR4 and TLR9 in skin structures was conducted by histochemical method with the use of monoclonal antibodies. The authors found increased expression of TLR2 and TLR4 in the epidermal cells and vascular endothelial cells of psoriasis patients in the absence of expression of TLR9. According to the authors, it contributes to the development of chronic inflammatory reactions.

Some authors [22] studied the association of polymorphisms TLR2 and TLR9 genes with preterm labor infectious origin and intrauterine infection. Single nucleotide polymorphisms (SNP) TLR2 genes were identified in clinical samples by PCR and SNP TLR9 gene was determined by PCR in real time. It is shown that the Arg allele polymorphic marker gene TLR2 Arg753Gln was associated with intrauterine infection. Another allele A polymorphic marker gene A2848G TLR9 associated with urgent delivery when urogenital infection.

Other authors [23] summarized information about the role of Toll-like receptors (TLR) and their ligands in the pathogenesis of atherosclerosis. Bacterial lipopolysaccharide (LPS), may interact with TLR4 and induce the formation of atherosclerotic lesions in the arterial wall. The risk of atherosclerosis is reduced by mutational damage TLR4. Other microbial ligands and heat shock proteins may also be involved in the induction of atherosclerosis. Proposed a unified theory of atherogenesis, according to which the induction and progression of atherogenesis is a side effect of the interaction of exogenous and endogenous ligands to TLR.

Researchers [24] studied TLR-mediated functional activity of peripheral blood mononuclear cells of children with various forms of neutropenia. The authors found that ligands TLR2, TLR4, TLR5 has an increased catalytic activity on TNF production by mononuclear cells in children with congenital neutropenia, and do not affect the immune mononuclear cells of children with neutropenia. Statistically significant increase IFNa output in response to ligands TLR3, TLR8 and TLR9 in children with immune neutropenia is shown. The authors believe that the identified changes in TLR-mediated functional activity of mononuclear cells in children with various forms of neutropenia may be essential in the development and course of infection in these patients. Researchers also [25] determined TLR expression in the spleen and lymph nodes of mice by mucosal immunization methods. Immunization of mice with multicomponent vaccine "Immunovac" was carried out in mucosae and subcutaneous. Based on these data, the authors believe that the different degree of sensitization by different routes of administration of the same drug is

predetermined at the stage of the interaction of the ligand with the TLR. Researchers [26] studied the value of expression of TLR for selecting pharmacological correction of cervical pathology and endometrium. After treatment with sodium nucleinate increase in the frequency of cells expressing TLR4 and TLR9 types in the material, as well as reducing the number of human papillomavirus oncogenic risk was observed. Other authors [27] studied the effect of cyclooxygenase inhibitors on mediated TLR the production of pro-inflammatory and anti-inflammatory cytokines in peripheral blood mononuclear cells from healthy donors and patients with acute pancreatitis. It is shown that cyclooxygenase inhibitors inhibit TLR-mediated production of both pro-inflammatory cytokines (IL-1, 6, 8, 12 and TNF), and anti-inflammatory cytokine IL-10 by these cells. The using of cyclooxygenase inhibitors in patients with acute pancreatitis on the initial stage of the disease reduces the TNF production in peripheral blood mononuclear cells in response to lipopolysaccharides (LPS). Accordingly, this leads to decrease effector function and TLR4 TLR1 / 2 of these patients that reduce the risk of complications. Determination of the expression of TLR and their functional activity is the first step in the evaluation of TLR in humans. For complete information about the system TLR comprehensive assessment of all its units is required. Such an approach was formulated earlier for assessing the immune status on pathogenetic principle. It was proposed to evaluate the various stages functioning of immune system [3]. Further evaluation stages TLR system must include an analysis of all other TLR system components, such as an estimation expression of molecules involved in signal transduction, transcription factors, etc. It will allow to specify and localize molecular defects in the innate immune system, as well as to assess their role in the pathogenesis of a wide range of diseases. Great contribution to the study of this problem can make experimental studies using transgenic and gene-knockout mice with different gene defects in order to better determine the effect of the expression of TLR polymorphisms and susceptibility to various, including infectious diseases. There is also of particular interest to study the individual paths where the specific adapter proteins for each TLR are used, as this would enhance our understanding of the body's response to different ligands TLR [15].

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КЕЙБІР АУРУЛАРДЫҢ ПАТОГЕНЕЗІНДЕГІ ПАТТЕРН-ТАНУШЫ РЕЦЕПТОРЛАРДЫҢ МАҢЫЗЫ

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Тірек сөздер: паттерн-танушы рецепторлар, жұқпа, туа біткен иммунитет.

Аннотация. Шолуда туа біткен иммунитеттің мембранамен байланықан рецепторлары – Толл-тәрізді рецепторлар туралы негізгі түсініктеме, оларды анықтаудың негізгі әдістері, экспрессиясының клиникалық зерттеулері, сонымен қатар олардың көмегімен алынған нәтижелердің негізгі анықтаулары қарастырылған. Зерттеулердің болашағы TLR жүйесінің қызметі туралы толық мағлұмат алуға негізделген, сонымен қатар оның барлық звеноларын кешенді бағалау қажет. Бұл туа біткен иммунитет жүйесінің бұзылыстарының молекулалық ақауларын нақтылауға жағдай туғызып отыр, сонымен қатар көптеген аурулардың патогенезінде олардың қызметін бағалауға мүмкіндік береді.

РОЛЬ ПАТТЕРН-РАЗПОЗНАЮЩИХ РЕЦЕПТОРОВ В ПАТОГЕНЕЗЕ НЕКОТОРЫХ ЗАБОЛЕВАНИЙ

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Ключевые слова: паттерн-распознающие рецепторы, инфекция, врожденный иммунитет.

Аннотация. В обзорной статье рассматриваются основные понятия о мембраносвязанных рецепторах врожденного иммунитета – Толл-подобных рецепторах, основные методы определения их экспрессии, применяемые в клинических исследованиях, а также полученные с их помощью результаты. Перспективы будущих исследований основаны на получении полной информации о функционировании системы TLR, также необходима комплексная оценка всех ее звеньев. Это позволит уточнить и локализовать молекулярные дефекты нарушений в системе врожденного иммунитета, а также оценить их роль в патогенезе и лечении широкого круга заболеваний.

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