THE INTERLEUKIN-17 FAMILY IN PNEUMONIA

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In this review, we described the biological functions of IL-17, including IL-17-mediated responses to signal transmission pathways, and the clinical significance of this cytokine in pneumonia. The key role of proinflammatory cytokines of the interleukin-17 family in the pathophysiology of the immune response in inflammatory processes, including pneumonia caused by pathogens of bacterial and viral origin, has been analyzed. Signalling pathways that induce the involvement of neutrophils, macrophage-monocyte cells in the inflammatory process, the production of interleukins involved in the elimination of pathogens are described. The significance of the imbalance of the cytokine profile of the interleukin-17 family for the prognosis of pneumonia in children is discussed. Over the past two decades, information has expanded about the IL-17 cytokine family as a pleiotropic group of molecules that act in a wide range, both in protective and pathological processes occurring mainly in the mucous membranes. The protective effects of IL-17 expression are especially important for the lungs, where there are many foreign agents. IL-17 plays an important role in protecting against extracellular bacteria and fungi as well as viruses that infect the cells of the mucous membranes. IL-17 helps activate epithelial cells to recruit neutrophils; effective removal of pathogens by neutrophils can limit the development of pneumonia caused by bacteria and fungi. However, in the case of persistent infections or chronic viral infections, prolonged release of IL-17 can have negative consequences, contributing to the constant attraction of neutrophils and eosinophils, degranulation and destruction of tissues. Identification of IL-17 responses is crucial for protection against pneumococcal infection, which has led to significant efforts to develop effective vaccines to enhance these responses.

Key words: IL-17, pneumonia, Th-17, immune responses.

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Introduction

Pneumonia in children in the XXI century is remaining an urgent health problem in all countries over the world, as it is still the most common nosological group in the paediatric population and the structure of mortality from respiratory diseases. One of the leading causes of severe and atypical pneumonia is currently considered to be a change in the body immunological responses. At the present stage of understanding the pathogenesis of pneumonia, the state of immunity and the importance of immune disorders in the clinical picture, diagnosis and prognosis of the course of the disease are not completely clear. The study of the role of proinflammatory cytokines in the immune and inflammatory response is an important area of modern immunology [1, 2].

It has recently been shown that Th17 cells characterized by the production of IL-17, play an important role in the pathogenesis of inflammatory processes and protect the body from infectious diseases [3]. The IL17 family includes 6 cytokines: IL17A, IL17B, IL17C, IL17D, IL17E (IL25) and IL17F. The most powerful "pro-inflammatory" activity is IL17A (as well as IL17F), which is a "marker" cytokine of Th17 cells. IL17B, IL17C and IL17D are also classified as "pro-inflammatory" cytokines, while IL17E (also known as IL25), on the contrary, participate in the generation of Th2 cells and inhibit the activation of Th17 cells. The IL17 receptor family (IL17R) is a unique type of receptor consisting of 5 subunits (IL17RA → IL17RE) that share a common transmembrane domain. Binding of IL17 to the corresponding receptor induces the activation of transcription factors - NF-kB (nuclear factor kappalight-chain-enhancer of activated B cells), C/EBP (CCAT/enhancer-binding proteins) and AP1 (activation protein-1), etc., thus regulating the function of genes of many "pro-inflammatory" cytokines [4, 5]. In this review, we describe the biological functions of IL-17, including IL-17-mediated responses to signal transmission pathways, and the clinical significance of this cytokine in pneumonia course.

Biological functions of IL-17 and its pathophysiological significance in inflammatory processes

The first identified member of the IL-17 family was cloned in 1993 and was originally called cytotoxic T-lymphocytic antigen 8 [6]. The IL-17 binding receptor (IL-17RA) was identified later in 1995. Screening of homologous genes caused the discovery of five other highly conservative members of the IL-17 family (from IL-17A to IL-17F) [7]. The biological effects of IL-17B, IL-17D remain poorly understood. On the contrary, the pro-inflammatory properties of IL-17A and IL-17F are well characterized. Despite the high homology of IL-17A and IL-17F, thirteen different amino acid residues were found in the area of contact with the receptor [8].

IL-17 is produced mainly by a special class of CD4+ lymphocytes - T-helper-17, which play an important role in various immunosuppression reactions. In inflammatory diseases, the development of Th-17 cells, including clonal expansion and stabilization of the IL-17A phenotype, depends on IL-23. IL-23 increases the population of Th17 cells and is recognized as a
powerful inducer of IL-17A. Recent studies show that the so-called “IL-17/IL-23 axis” is a key element of inflammation and is involved in immune responses to fungal and bacterial infections and in the pathogenesis of autoimmune diseases. IL-17A-mediated inflammation is necessary to protect the body from various infections [9]. At the same time, IL-17A, being involved in immunopathological processes, can also aggravate inflammatory reactions of the fetus. The level of IL-17A increases in various inflammatory conditions, including pneumonia, sepsis and systemic lupus erythematosus, rheumatoid arthritis [5].

IL-17 can be produced by a wide range of cell populations, including Th17 cells, γς T cells, NK cells, group 3 congenital lymphoid cells (ILC3S), CD8+ cells (Tc17), neutrophils, migroglia and mast cells. IL-23 and ROR γt are necessary for all types of cells producing IL-17 [10]. Th17 cells produce a variety of inflammatory cytokines, including granulocyte-macrophage colony stimulating factor (GM-CSF), IL-21 and IL-22. Th17-induced responses are involved in protecting the body from infections, inflammatory and autoimmune disorders. Other major sources of IL-17 include myeloid cells (e.g., kidneys and lungs) and Pannet cells in intestinal crypts [11]. In response to stress proteins, pathogen-associated molecular structures (RAMPS) or microbial metabolites, antigen presenting cells (APC) produce IL-23 and IL-18 to accelerate the release of IL-17. IL-17 levels depend on specific conditions, including pathogenicity, localization, and severity of infection [12].

IL-17 binds to five cytokine receptors (from IL-17RA to IL-17RE) on target cells to control their biological action. IL-17R is expressed in various cell populations, including keratinocytes, fibroblasts, mesothelial cells, epithelial cells and leukocytes [13]. All these receptors share a common SFER domain in the intracellular domain. IL-17RA is a common receptor for different isoforms of IL-17. IL-17 cytokines can trigger signals through the IL-17RA receptor complex. IL-17RB and IL-17RE serve as specific receptors for IL-17B and the heterodimeric IL-17RA/IL-17RB complex, respectively. IL-17A and IL-17F act through the same IL-17RA/IL-17RC receptor complex. IL-17A/IL-17C interacts with IL-17R to stimulate inflammatory reactions by activating mitogen-activated protein kinase (MARK), nuclear factor – kappa B (NF-KB) [14]. IL-17A can also transmit signals via the TOLL-IL-1 receptor (TIR).

IL-17A is the most well-studied member of the IL-17 family and interacts with several mediators (for example, GM-CSF, IFN-γ, IL-24, TNF-α), exerting its pro-inflammatory effect [9]. In general, IL-17A mediated downstream pathways induce the production of inflammatory mediators, chemokines, antimicrobial peptides (AMPs) and remodelling proteins. IL-17A has a decisive influence on the protective functions of the body, cell transport, immune modulation and tissue repair, playing a key role in the induction of innate immune defence. IL-17A stimulates non-hematopoietic cells (epithelial cells), and then acts independently or synergistically with additional pro-inflammatory mediators, contributing to the production of chemokines, granulocyte-colony stimulating factor, thereby attracting myeloid cells to areas of inflammation [15]. IL-17A also stimulates the release of IL-2 from Th17 cells, which in turn increases the number of regulatory T cells. IL-17A promotes the secretion of AMP (β-defensins, calgranulin, S100A8 lipocalin-2) from macrophages and neutrophils in response to acute invasion of pathogens. Moreover, IL-17A can induce nitric oxide synthesis (iNOS) and cyclooxygenase-2 (COA-2). According to a number of authors, IL-17A is crucial for maintaining the integrity and function of the mucosal barrier by increasing tight contacts and induction of acute phase proteins. IL-17A helps to control the remodelling of the airway vessels through the responses of Th17 cells in lung inflammation [11].

In addition, IL-17A plays a key role in the repair and remodelling of other tissues (heart, bone). IL-17B was initially identified as an anti-inflammatory mediator that accelerates the recruitment and migration of neutrophils. IL-17B suppresses the transmission of signals through IL-25 and weakens inflammation of the mucous membrane. IL-17C can be produced by different types of non-immune cells (epithelial, keratinocytes), providing protective functions of the intestine, skin and nervous system. IL-17C released from epithelial cells maintains the integrity of barriers after epithelial damage [8]. IL-17D is the least studied cytokine in the IL-17 family. Like other isoforms, IL-17D triggers the secretion of various inflammatory cytokines - IL-6, IL-8 and GM-CSF. A marked increase in IL-17D levels in viral infections has been shown.

Like IL-17A, IL-17E acts as a "mucosal barrier" molecule that provides immunity against parasitic infections [11]. Epithelial cells of the thymus contribute to the production of IL-17E and the protection of the body through the development of the T-cell receptor of congenital lymphoid cells type 2 (iNKT-2). IL-17E differs from other members of the IL-17 family. IL-17E controls stromal cells, type 2 T helper cells (Th2), epithelial cells and ILC2 [8]. It also accelerates the synthesis of thymus lymphopoietin (TSLP). IL-13, IL-5, IL-4 and IL-13 and reduces the levels of IL-23, IL-6 and IL-1. IL-17E is involved in the pathogenesis of parasitid and fungal infections, allergies and autoimmune diseases. In addition, IL-17E-mediated responses depend on the epithelium of the respiratory tract, mast cells, eosinophils and Th2 cells, thereby contributing to the immunopathogenesis of asthma [16].

IL-17F and IL-17A have similarities in receptors, signalling, functions, and cellular sources. Like IL-17A, IL-17F plays a crucial role in inflammatory reactions and maintenance of the mucosal barrier.
The role of IL-17 in protecting the lungs from bacterial and viral pathogens

Cytokines play an important role in maintaining normal tissue homeostasis in the lungs and regulate interactions between cells during inflammation in lung tissue. Phagocytes, in particular macrophages and neutrophils, are the main components of inflammatory and immunological reactions [1]. The development of inflammation in the lower respiratory tract involves the coordinated expression of pro- and anti-inflammatory cytokines. After recognizing the antigens of 32 microbes, TLR-mediated signal transmission leads to the production of IL-16 and TNF-α. Along with the above cytokines, IL-17 plays a significant role in the immunopathological processes responsible for the development and features of the course of pneumonia, the synthesis of which, as mentioned above, is induced by IL-17 and IL-23 [17]. Being a powerful proinflammatory cytokine, IL-17, interacting with the IL-17R receptor, promotes the release of C-X-C chemokines that cause the attraction of neutrophils into the lung tissue and their activation. The IL-17 family and related cytokines perform important endogenous functions on the surface of the mucous membranes, and the expression of these cytokines provides protection against a variety of extracellular pathogens. Mice with IL-17 deficiency are more susceptible to various respiratory pathogens, including K. pneumoniae, S. pneumoniae and P. Aeruginosa [18]. Pulmonary-associated bacterial load was higher in mice with IL-17 deficiency and the corresponding receptor, and mice with IL-17 gene knockout were characterized by an excessive inflammatory response and severity of the disease. Mice infected with S. pneumoniae with a deficiency of IL-23, which is a regulator of IL-17 production, were unable to produce IL-17 and IL-6 and had a higher bacterial load both in the lungs and in the blood. The transfer of neutrophils to the lesion was also disrupted in mice with IL-23 deficiency. This suggests that the deficiency of this cytokine was the cause of increased susceptibility to S. Pneumoniae [19]. Similarly, IL-17R -/- mice were extremely sensitive to K. pneumoniae and could not involve innate immune cells, such as neutrophils and macrophages in the inflammatory process, due to a decrease in the production of G-CSF and macrophage inflammatory protein (MIP-2). IL-17A levels are positively associated with tissue bacterial load in mice infected with Klebsiella pneumonia.

Interestingly, infection of P. aeruginosa mice caused the expression of another member of the IL-17 (IL-17C) family, IL-17A indirectly [13]. It is known that IL-17C is secreted by epithelial cells in response to stimulation of a Toll-like receptor by bacterial pathogens, transmitting an autocrine signal, which further enhances the expression of neutrophils, involvement of chemokines CXC CXCL1 and CXCL2 (KC and MIP-2) in the inflammatory process, facilitating bacterial clearance. It has recently been shown that the cellular source of IL-17 production, necessary for the protection and destruction of bacteria varies from pathogen to pathogen. It has been shown that IL-23-controlled expression of IL-17 from γδ T cells plays an important role in the elimination of K. pneumoniae [18]. Similarly, it has been shown that IL-17 produced from ILC3 cells is important for the elimination of K. pneumoniae TNF-α indirectly. It is believed that for purification from Pseudomonas, the predominant sources of IL-17 are ILC3, TH17 T cells and γδ T cells [20]. It is not yet clear how IL-17, produced by different cell types, can differ in its sensitivity to different pathogens. However, it is believed that IL-17 from any of these sources can stimulate epithelial cells to create chemokine gradients to attract immune cells such as neutrophils, which play an important role in cleansing the body of bacteria.

In the initial stage of acute pseudomonas infection, the main sources of IL-17 are Th17 cells, T lymphocytes and type 3 congenital pulmonary lymphoid cells (type 3 pulmonary innate lymphoid cells – pILC3) [21]. It was demonstrated [22] that 6 hours after the introduction of endotoxin into the respiratory tract, the level of IL-17 in the bronchoalveolar fluid increases, and anti-IL-17 antibodies completely inhibit the recruitment of neutrophil granulocytes into the respiratory tract. Xilin Xu and co-authors [23] indicate that IL-17 mRNA expression is significantly increased during acute pneumonia caused by Pseudomonas aeruginosa. An increase in the concentration of IL-17 is observed in the bronchoalveolar fluid, but not in the blood serum of infected individuals. In mice with lipopolysaccharide induced acute respiratory syndrome (ARDS), IL-17A levels were also elevated in plasma, lung tissue lysate, and bronchoalveolar lavage fluid [24]. Accordingly, patients with ARDS caused by sepsis retain high levels of IL-17A, which makes it possible to use IL-17A as a biomarker for assessing the severity and prognosis of the disease. Moreover, activation of IL-23/IL-17 signalling has a negative effect on lung inflammation caused by sepsis.

Along with IL-8 when the lung tissue is infected with pseudomonas infection, IL-17 promotes the production of IL-17, MIP-2 and G-CSF involved in the recruitment of neutrophils [23]. The level of IL-17 correlates with the degree of infiltration of the affected tissue by neutrophils, the effectiveness of bacterial clearance and the survival of infected individuals. It is assumed that IL-17 functions primarily as a component of the mechanisms of the local immune response of pneumonia caused by Pseudomonas aeruginosa. In IL-17A and IL-17RA knockout mice, there is an increased incidence of infections induced by Pseudomonas aeruginosa, reduced bacterial clearance and a high risk of chronization of the process. Considering the negative effect of IL-17RA receptor deficiency on
the course of Pseudomonas aeruginosa infection, it is believed that the resistance of the macroorganism to Pseudomonas aeruginosa is mediated by both IL-17A and IL-17F, which implements its action through IL-17RA. Patricia J. Dubin and Jay K. Kolls [25] showed that although the neutralization of IL-17 leads to a decrease in the concentration of proinflammatory cytokines, neutrophil granulocytes in infiltrated lung tissue and a decrease in bacterial load, it is accompanied at the same time by a lighter clinical course and a decrease in the risk of developing morphologically significant lung damage. Hyperproduction of IL-17 contributes to an increase in the levels of chemokines responsible for the massive influx of neutrophil granulocytes, which can lead to the destruction of lung tissue. Of interest is the fact that, unlike other pro-inflammatory cytokines, in particular IFN-γ, whose high concentration is characteristic only in acute infection, the level of IL-17A remains high in the chronic inflammatory process induced by Pseudomonas aeruginosa [26]. Thus, IL-17 increases the activity of bacterial clearance and survival in pseudomonas infection by increasing the recruitment of neutrophil granulocytes into the lesion and plays a protective role in the early stage of acute pseudomonas infection of the lungs. A number of studies have shown that IL-17 contributes to the development of host immunity against the influenza virus [5]. In mice infected with the influenza virus, IL-17 deficiency was associated with increased mortality. In addition, IL-17A is involved in the immunopathogenesis of acute lung injury caused by the influenza A (H1 N1) virus. Mice with IL-17 deficiency after influenza are also more susceptible to the development of bacterial pneumonia caused by S. aureus and S. pneumoniae [27]. It has been shown that the influenza A virus significantly suppresses IL-18 signals, which reduces the expression of IL-17, which is critically necessary for the clearance of S. Aureus. Similarly, mice with IL-1 receptor deficiency had a significantly higher bacterial load, and subsequently developed more severe pneumonia after infection with the influenza virus. Interestingly, a specific micro-RNA, MIR-155, is predominantly induced by influenza infection, reducing the expression of IL-23 and IL-17, which leads to a decrease in bacterial clearance and an increase in the severity of bacterial S. aureus pneumonia. In addition, mice with a deficiency of IL-22, which is a regulator of IL-17, showed increased damage to epithelial cells and fibrosis after infection with the influenza virus. Mice deficient in IL-22 were also more susceptible to post-influenza bacterial pneumonia caused by S. pneumoniae, which led to a more severe IFNγ response and increased mortality. The IL-17A-mediated response correlates with the severity of the disease after infection with Epstein-Barr virus (EBV), Herpes simplex virus (HSV), respiratory syncytial virus (RSV), smallpox vaccine virus and hepatitis virus.

Depletion of IL-17R mitigates inflammation and reduces the influx of neutrophils, preventing infection with influenza [28]. The protective or pathological role of IL-17 in viral infections remains controversial.

Thus, IL-17A forms part of the alarm signal of the “watchdog” cells to stimulate the host’s defense. There is increasing evidence that IL-17A is involved in the pathogenesis of pneumonia in relation to the regulation of inflammatory and immune responses. On the one hand, IL-17A interacts with various mediators (for example, TNF-α, IL-1, IL-6) to activate neutrophils infiltrating tissue to eliminate invading pathogens. On the other hand, IL-17A, when interacting with other pro-inflammatory cytokines, causing a cascade of immune reactions, leads to hyperinflammation with harmful consequences for the host organism. Accordingly, the increased level of IL-17A seems to be associated with the severity of the disease in pneumonia. Accordingly, IL-17A can be either protective or pathogenic, depending on the specific circumstances. Further studies are necessary for in-depth study of the pathogenic mechanisms of IL-17A’s effect on different immune responses in pneumonia in different clinical situations.

The role of cytokines in Th17 and Treq pathways

The human immune system is a tightly regulated network that protects the body from various diseases. An important aspect in maintaining immune homeostasis is the balance between pro-inflammatory Th17 cells and anti-inflammatory T-regulatory (Treq) cells. An imbalance between Treq and Th17 cells can lead to serious pathology in many organs and tissues [29].

Experimental studies have shown that differentiation of Treq and Th17 from naive (who had no contact with the antigen) CD4+ T cells is regulated reciprocally. Th17 cells differentiate in the presence of IL-6 and TGF-β. Although IL-23 was initially thought to be a key component of the Th17 differentiation pathway, recent studies have shown that this cytokine is crucial for the growth, survival, and stability of this subgroup of T helper cells. These cytokines control the signal converter and activator of the transcription pathway, which is important for the differentiation of Th17 cells. After differentiation, these cells express a unique transcription factor and secrete a characteristic cytokine profile, including IL-17A, IL-17F, IL-21, TNF-α and IL-22 [30]. The role of cytokines in the modulation of the Th17/Treq pathway has been confirmed by many studies [27]. It is known that although Th17 cells have pathogenic properties, not all actions of Th17 cells are harmful; they have also been shown to provide protection against infections caused by extracellular bacteria such as Streptococcus pneumoniae.

The gram-positive bacterium S. pneumonia (pneumococcus) causes significant morbidity and mortality among children under five years of age.
worldwide [31] due to a number of diseases, including meningitis, bacteremia and pneumonia. The importance of CD4+ Th17 cells in protecting the mucous membrane from pneumococcal infections is becoming increasingly obvious. Many studies confirm the key role of Th17 responses in preventing or reducing the carriage of pneumonia in mouse and human models. Th17 cells secrete the proinflammatory cytokine IL-17, which is important for the recruitment and activation of macrophages and neutrophils in the nasopharynx, which, in turn, is crucial for the elimination of this pathogen from the host body [32].

Colonization of the nasopharynx, which in most cases is asymptomatic, is the first step in the pathogenesis of the disease. It causes an inflammatory reaction that is not regulated, can lead to excessive damage to the mucous membrane with the spread of the process to the underlying parts of the respiratory system and facilitate the transmission of infection between people. Th17 mediated immunity is a key factor of protection against colonization and lung pathology, whereas the presence of serotype-specific IgG is a correlate of vaccine-induced protection against invasive diseases [33]. The importance of IL-17 secreting Th17 cells was highlighted by the discovery demonstrating that these cells organize the recruitment and activation of neutrophils, monocytes and macrophages in the foci of inflammation in the upper respiratory tract, which leads to the removal of pneumococci. Moreover, prior colonization induces both systemic IgG and lung response to IL-17A, which shortens the duration of subsequent carrier events and inhibits the development of invasive pneumococcal disease. Although systemic and mucosal antibodies also perform protective functions, the protection against lung infection provided by previous colonization is lost in the absence of CD4+ T cells or IL-17. It was found that the site of subsequent infection determines the basis for protection, Th17 responses are critical against lung infection, whereas antibodies are necessary against invasive infection [7]. However, IL-17-based protection against pneumococcal infection seems to be reduced or lost when it is preceded by an infection caused by the influenza virus [34]. The reasons for this are not fully understood; although this may be due to the inclusion of viral activation of interferon signalling, which in turn negatively regulates IL-17 responses to bacterial infections. Therefore, an important area of future research is how IL-17A responses can be modulated in the presence of viral infections, especially influenza or respiratory syncytial virus.

The protective role of IL-17 in humans is confirmed by the following original results: IL-17 is produced after in vitro stimulation of mononuclear cells of the tonsils and peripheral blood by pneumococcal antigens, such as pneumolysin and whole cell antigen. The protective effect of IL-17 is mediated by enhanced opsonophagocytic destruction of pneumococci by human neutrophils in the absence of antibodies and complement and is cancelled in the absence of IL-17A receptors. Moreover, a number of studies indicate that high concentrations of IL-17 are associated with a low carrier density of pneumococci in the nasopharynx in mice and children. Recently, it was found that mucosal Treq isolated in children with pneumococcal carrier are more numerous than in children without pneumococcal carrier, and exhibit strong inhibitory effects on the proliferation of CD4+ T cells. Interestingly, compared to children who are not colonized, young children (<6 years old) colonized with pneumococcus have significantly more Treq with effector phenotype, memory phenotype, which suppress the reactions of pneumococcal T cells in their adenoids or tonsils. Stimulation by the whole-cell antigen of pneumococcus causes the proliferation of Treq and the production of IL-10, but not IL-17. These changes completely after the depletion of Treq, which leads to the secretion of IL-17. Moreover, the amounts of Th17 and Treq in the lymphoid tissue associated with the nose are negatively correlated; the amount of Th17 increases with age and becomes greater in individuals without a carrier [35]. In contrast, mice resistant to pneumococcal pneumonia have significantly more Treq in their lungs than mice with invasive pneumonia, and this is mediated by the transmission of TGF-β signals. These data suggest that maintaining Th17/Treq balance is critically important for controlling pneumococcal colonization. Additional studies are needed to confirm these effects in pneumococcal infection and human disease.

Identification of IL-17 responses is crucial for protection against pneumococcal infection, which has led to significant efforts to develop effective vaccines to enhance these responses [36].

**Conclusion and prospects for further research**

Over the past two decades, information has expanded about the IL-17 cytokine family as a pleiotropic group of molecules that act in a wide range, both in protective and pathological processes occurring mainly in the mucous membranes. The protective effects of IL-17 expression are especially important for the lungs, where there are many foreign agents. IL-17 plays an important role in protecting against both extracellular bacteria and fungi, as well as viruses that infect the cells of the mucous membranes. IL-17 helps activate epithelial cells to recruit neutrophils; effective removal of pathogens by neutrophils can limit the development of pneumonia caused by bacteria and fungi. However, in the case of persistent infections or chronic viral infections, prolonged release of IL-17 can have negative consequences.

The literature review confirms that IL-17 plays a central role in inflammatory processes and
therefore the regulation of its functioning is of great importance for the body. Single data on the role of predictors and features of the functioning of the IL-17 system in pneumonia in children are presented, which determines the relevance of further research.

References
цитокінів IL-17 як про плейотропну групу молекул, що діє у широкому спектрі як у захисних, так і у патологічних процесах, що протікають, в основному, в слизових оболонках. Захисні ефекти експресії IL-17 особливо важливі для легень, де багато чужорідних агентів. IL-17 відіграє важливу роль у захисті від позаклітинних бактерій, грибів, а також вірусів, що вражають клітини слизових оболонок. IL-17 допомагає активувати епітеліальні клітини для рекрутування нейтрофілів; ефективне видалення патогенів нейтрофілами може обмежити розвиток пневмонії, спричиненої бактеріями та грибами. IL-17 збільшує активність бактеріального клірування та виживаність при синьогнійній інфекції за рахунок збільшення рекрутування нейтрофільних гранулоцитів у вогнищі ураження, та відіграє захисну роль на ранній стадії гострої синьогнійної інфекції легень. Однак у разі спільної інфекції або при хронічних вірусних інфекціях тривале вивільнення IL-17 може мати негативні наслідки, сприяючи постійному залученню нейтрофілів та еозинофілів, дегрануляції та руйнуванню тканин. Ідентифікація відповідей IL-17 має вирішальне значення для захисту від пневмококкової інфекції, що привело до значних зусиль розробки ефективних вакцин для посилення цих відповідей.

Реферат

СЕМЕЙСТВО ИНТЕРЛЕЙКИНА-17 ПРИ ПНЕВМОНИИ
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Ключевые слова: IL-17, пневмония, Th-17, иммунные реакции.

В настоящем обзоре описаны биологические функции IL-17, включая опосредованные IL-17 ответы на пути передачи сигнала, клиническую значимость указанного цитокина при пневмонии. Проанализирована ключевая роль бактериальных цитокинов семейства интерлейкинов 17 в патофизиологии иммунного ответа при воспалительных процессах, в том числе при пневмонии, вызванной возбудителями бактериального и вирусного происхождения. Описаны сигнальные пути, индуцирующие вовлечение нейтрофилов, клеток макрофагально-моноцитарного ряда в воспалительный процесс, продуцирующие интерлейкины, участвующие в элиминации возбудителей. Обсуждается значимость дисбаланса цитокинового профиля семейства интерлейкина-17 для прогноза течения пневмонии у детей.

За последние два десятилетия расширились сведения о семействе цитокинов IL-17 как о плейотропной группе молекул, которые действуют в широком спектре, как в защитных, так и в патологических процессах, протекающих, в основном, в слизистых оболочках. Защитные эффекты экспрессии IL-17 особенно важны для легких, где много чужеродных агентов. IL-17 играет важную роль в защите как от внеклеточных бактерий, так и от грибов, а также от вирусов, поражающих клетки слизистых оболочек. IL-17 помогает активировать эпителиальные клетки для рекрутирования нейтрофилов; эффективное удаление патогенов нейтрофилами может ограничить развитие пневмонии, вызванной бактериями и грибами. IL-17 увеличивает активность бактериального клиренса и выживаемость при синегнойной инфекции за счет увеличения рекрутирования нейтрофильных гранулоцитов в очаг поражения и играет защитную роль на ранней стадии острых синегнойных инфекций легких.

Однако в случае хронических инфекций или при хронических вирусных инфекциях длительное высвобождение IL-17 может иметь отрицательные последствия, способствуя тому привлечению нейтрофилов и зонофилов, дегрануляции и разрушению тканей. Идентификация ответов IL-17 имеет решающее значение для защиты от пневмококковой инфекции, что привело к значительному усилиям по разработке эффективных вакцин для усиления этих ответов.