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# Potential biochemical markers of chronic bronchitis

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**ABSTRACT**

The review systematizes modern data on the biochemical markers that can clarify the nature and the course of chronic bronchitis. The article describes the markers associated with bronchopulmonary pathology, such as tumor necrosis factor alpha (TNFα), interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-10 (IL-10), tissue factor, type 1 plasminogen activator inhibitor (PAI-1), and monocyte chemoattractant protein-1 (MCP-1). For each biomolecule, its properties, functions, direct role in body processes, and associations with bronchopulmonary pathology are described. The use of these markers for early diagnosis of bronchopulmonary pathology and monitoring of the treatment effectiveness is promising and requires further in-depth study.

**Key words:** chronic obstructive pulmonary disease, chronic bronchitis, biochemical markers, tumor necrosis factor alpha, interleukin-1, interleukin-6, interleukin-8, interleukin-10, tissue factor, type 1 plasminogen activator inhibitor, monocyte chemoattractant protein 1.

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# Потенциальные биохимические маркеры хронического бронхита

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**РЕЗЮМЕ**

В обзоре систематизируются современные данные о биохимических маркерах, которые расширяют наше понимание о закономерностях развития хронического бронхита. В статье приведены маркеры, ассоциированные с патологией бронхолегочной системы: фактор некроза опухоли альфа; интерлейкин (ИЛ) 1, 6, 8, 10; тканевой фактор; ингибитор активатора плазминогена 1-го типа; моноцитарно-хемоаттрактантный протеин 1. Для каждой представленной биомолекулы описаны ее свойства, функции, непосредственная роль в организме, взаимосвязи с патологией бронхолегочной системы. Использование

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данных маркеров целесообразно для ранней диагностики, контроля лечения и требует более глубокого изучения.

**Ключевые слова:** хронический бронхит, хроническая обструктивная болезнь легких, биохимические маркеры, фактор некроза опухоли альфа, интерлейкин 1, интерлейкин 6, интерлейкин 8, интерлейкин 10, тканевой фактор, ингибитор активатора плазминогена 1-го типа, моноцитарно-хемоаттрактантный протеин 1.

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## INTRODUCTION

At the moment, diseases of the bronchopulmonary system have gained enormous prevalence not only in Russia but throughout the world. Chronic bronchitis (CB) occupies a leading position among chronic non-specific lung diseases. According to various estimates, the number of patients with CB in Russia is about 33 million people. According to the WHO recommendation and Russian clinical guidelines, CB is a chronic diffuse progressive inflammation of the bronchi, manifested by productive cough lasting at least three months a year for two consecutive years, with the exception of other diseases of the upper respiratory tract, bronchi, and lungs, which could cause these symptoms. Chronic obstructive pulmonary disease is not a single, specific disease, but a collective term used to describe chronic lung diseases that restrict airflow to the lungs. A combination of chronic bronchitis CB with emphysema is defined as chronic obstructive pulmonary disease (COPD).

However, at the moment, CB occurs as an independent disease, which may not be associated with obstruction. According to the WHO, today, respiratory diseases are the third leading cause of death in the world with about 2.8 million people dying every year, which accounts for 4.8% of all causes of death. The prevalence of CB varies throughout the world, ranging from 3.4 to 22.0% in the general population up to 74.1% in patients with COPD [1–3].

In the largest study of current or former smokers without airflow obstruction (4,900 participants), 12.2% of people had CB using the classical definition [4]. A recent European study showed that the prevalence of CB was 18% in 972 patients with COPD [5]. A Chinese study of 1,668 patients with COPD showed that 30% of participants met the diagnostic criteria for CB [6]. Therefore, it is important to understand the need for earlier diagnosis of these diseases and the search for possible predictors and ways of influencing the pathogenesis of respiratory pathology. The data below describe promising biochemical markers which, according to available literature, may have diagnostic benefits in examination of pulmonary pathology.

## TUMOR NECROSIS FACTOR

Tumor necrosis factor (TNF, cachexin or cachectin, TNFα) is a cellular acute-phase signaling protein involved in systemic inflammation and one of the representatives of the cytokine family. It is produced by macrophages, lymphocytes, natural killer cells, neutrophils, mast cells, eosinophils, neurons, etc. [7]. TNF is synthesized as a type II membrane protein, with a molecular weight of 26 kDa (233 amino acids). It is released via proteolytic cleavage by the TNF-converting enzyme (a disintegrin and metalloprotease 17 (ADAM17)), soluble TNF with a molecular weight of 17 kDa (157 amino acids) is cleaved from the membrane-binding fragment.

The TNF family includes TNF-alpha, TNF-beta, CD40 ligand (CD40L), Fas ligand (FasL), TNF-related apoptosis-inducing ligand (TRAIL), and LIGHT (homologous to lymphotoxins) [8].

TNF has many important physiological and pathological effects. TNF causes necrosis of tumor cells (a process that includes swelling of cells, destruction of organelles, and lysis of cells) and apoptosis (a process that involves contraction of cells, formation of condensed bodies, and DNA fragmentation).

In addition, TNF is a key mediator of both acute and chronic systemic inflammatory responses. TNF not only induces its own secretion, but also stimulates

the production of other inflammatory cytokines and chemokines. TNF plays a central role in autoimmune diseases, such as rheumatoid arthritis (RA), inflammatory bowel diseases (IBD), including Crohn's disease and ulcerative colitis, multiple sclerosis, systemic lupus erythematosus, and systemic sclerosis [9–11].

There is a rather large and extensive knowledge base on the association between TNF and CB. Over the past 20 years, several extensive fundamental meta-analyses on this topic have been published, which did not come to a single conclusion. Thus, according to W. Gan et al., TNF has a pronounced correlation between its serum level and the severity of CB [12].

A number of centers stated that there was no significant correlation between TNF and CB, however, in a detailed review of the findings, it was concluded that at early stages of CB, the correlation between markers of inflammation and the degree of impaired respiratory function was poorly significant [13].

Recent studies by Y. Mosrane et al. demonstrated a higher correlation with TNF in smoking CB patients than in the group of non-smokers [14].

When assessing biochemical markers during treatment, a significant direct correlation was found between the response to COPD treatment and the TNF level in the blood [15].

Therefore, at present, TNF in patients with CB is a promising biochemical parameter that requires a more in-depth analysis as a biomarker and a target during treatment in COPD patients.

## INTERLEUKIN-1

Interleukin-1 (IL-1) is one of the most important cytokines of innate immunity and inflammation. The IL-1 family includes 7 ligands with proinflammatory activity: IL-1α and β, IL-18, IL-33, IL-36α, β, γ, three receptor antagonists (IL-1Ra, IL-36Ra, IL-38), and an anti-inflammatory cytokine (IL -37). The IL-1 receptor (IL-1R) family includes 6 receptor chains forming 4 receptor complexes, two decoy receptors (IL-1R2, IL-18BP), and two negative regulatory receptors (TIR 8, IL-1RAcPb). Strict regulation by receptor antagonists, decoy receptors, and signal transduction inhibitors provides a balance between enhanced innate immunity and uncontrolled inflammation [16].

The most studied representatives of this family at the moment are IL-1α and IL-1β. The precursor IL-1α is constantly present in the epithelial layers of the entire gastrointestinal tract, lungs, liver, kidneys, endothelial cells, and astrocytes. In cell death from necrosis, as occurs in diseases associated with local or global ischemia, the precursor IL-1α is released. Thus, IL-1α mediates early phases of sterile inflammation by rapidly initiating a cascade of inflammatory cytokines and chemokines and functions as an alarmin [17].

In contrast, IL-1β is produced by hematopoietic cells, such as blood monocytes, tissue macrophages, dendritic skin cells, and brain microglia, in response to Toll-like receptors (TLR), activated complement components, and other cytokines (Table) [18].

Table

| Members of the IL-1 family | | |
|---|---|---|
| Interleukin | Receptor | Function |
| IL-1α, IL-1β | IL-1R1 | Proinflammatory |
| IL-1β | IL-1R2 | Anti-inflammatory |
| IL-1ra | IL-1R1 | Anti-inflammatory |
| IL-18 | IL-1R5 | Proinflammatory |
| IL-33 | IL-1R4 | Proinflammatory |
| IL-36α, β, γ | IL-1R6 | Proinflammatory |
| IL-36Ra | IL-1R6 | Anti-inflammatory |
| IL-37 | IL-1R5 | Anti-inflammatory |
| IL-38 | IL-1R6 | Anti-inflammatory |

Members of the IL-1 family regulate most cells of the innate immunity, including macrophages, neutrophils, eosinophils, basophils, and mast cells. Based on this, control over IL-1 in patients with CB is considered justified. Although the pathogenesis of COPD has not been fully studied and is still under discussion, it is known that chronic inflammation caused by constant exposure of the respiratory tract and lung parenchyma to cigarette smoke is a leading cause of COPD [19]. In a mouse model, N.S. Pauwels et al. showed an increase in the level of IL-1 in mice with long-term exposure to cigarette smoke compared to the control group. Later, the study in humans confirmed the data obtained in mouse models in lung tissue samples, as well as in the induced sputum of patients with COPD: the IL-1 level was significantly increased compared to the healthy controls [20].

The serum levels of IL-1β were also higher in patients with COPD than in the healthy controls. The level of the inflammatory mediator in the serum correlated with important clinical parameters for controlling the course of the disease, such as airflow limitation, smoking status, C-reactive protein (CRP), serum neutrophilia, etc. [21].

The levels of inflammatory markers, such as procalcitonin, CRP, CCL17, TNF and IL-1β, were analyzed depending on the type of CB exacerbation. A pronounced correlation was found between the severity of the exacerbation and the level of IL-1β. The

authors also came to the conclusion about a more significant correlation with bacterial inflammation and ventilator-associated pneumonia (VAP), which complicated the course of CB exacerbation [22].

A very promising research area is phenotyping of the *NLRP* gene depending on the level of IL-1β. So, studies by P. Ozretić not only proved an increase in IL-1β in the group of patients with CB compared to the healthy controls, but also traced the IL-1β level depending on the *NLRP* gene polymorphism. It was found that homozygosity for the main alleles was associated with a lower concentration of IL-1 [23].

Phenotyping of *NLRP* is of great scientific interest, since it makes it possible to detect various risk groups for developing bronchopulmonary pathology, on the whole, and CB, in particular.

## INTERLEUKIN-6

Interleukin-6 (IL-6) is a member of the cytokine family which has proinflammatory and anti-inflammatory properties. IL-6 is encoded by the *IL-6* gene. Human IL-6 consists of 212 amino acids, including a signal peptide with 28 amino acids. Its gene is mapped to the chromosome 7, locus 7p15-21-q21. A segment of DNA in the regulatory region of this gene at position –572, where guanine (G) is replaced by cytosine (C), is called a genetic marker G (-572) C. The *IL-6* gene can exist in the form of two allelic variants, designated as the G-allele and the C-allele [24].

The cytokine is produced primarily by cells of the immune system, such as monocytes, lymphocytes, macrophages, endotheliocytes, microglia, and a number of non-immune cells, such as osteoblasts, myocytes, keratinocytes, synovial cells, chondrocytes, epithelial cells, folliculo-stellate cells of the pituitary gland, trophoblasts, vascular smooth muscle cells, etc.

IL-6 transmits signals through a complex of type I cytokine receptors on the cell membrane, consisting of a ligand-binding chain of IL-6Rα (CD126) and a signal-transmitting component, gp130 (also called CD130) [25].

IL-6 is responsible for stimulation of protein synthesis in the acute phase, as well as for neutrophilia. It supports the growth of B cells and is an antagonist of regulatory T cells. IL-6 can be secreted by macrophages in response to specific microbial molecules called pathogen-associated molecular pattern molecules (PAMPs). These PAMPs bind to an important group of detecting molecules of the innate immune system called pattern recognition receptors (PRRs), including Toll-like receptors (TLRs).

They are present on the cell surface and in intracellular compartments and induce intracellular signaling cascades that cause production of inflammatory cytokines [26]. In the light of recent data on the structure and functions of IL-6, studies have been conducted to identify the relationship between chronic obstructive and non-obstructive bronchitis. So, a recent longitudinal study, which investigated 1,843 participants for three years, demonstrated that an increased level of IL-6 was a prognostic factor in increasing mortality in chronic obstructive bronchitis [27]. Serum IL-6 level was significantly increased in the COPD groups compared to the healthy control [28, 29].

A. Agusti et al. demonstrated in the sample of 2,254 people that an increase in IL-6 associated with persistent inflammation was characterized by worse prognosis for CB [30].

A meta-analysis conducted by J. Wei et al. including at least 6,837 patients showed that serum IL-6 levels increased even in mild COPD, which may be the best marker for early inflammation and associated comorbidities. IL-6 is directly involved in inflammation and can be considered as a marker of mild systemic inflammation and an additional parameter for risk assessment along with smoking, the number of exacerbations, the frequency of hospitalization, and mortality [31]. Some authors point out contradictions with some studies that did not find significant differences in the level of IL-6 and the severity of the disease; however, most studies have a small sample [32, 33].

## INTERLEUKIN-8

Interleukin-8 (IL-8) is a member of the CXC chemokine subfamily. It is an important activator and chemoattractant for neutrophils and is involved in various inflammatory diseases. Numerous reports show that various cells express IL-8 mRNA and produce IL-8 protein, including monocytes, T-lymphocytes, neutrophils, fibroblasts, endothelial cells, and epithelial cells [34]. The human *IL-8* gene has a length of 5191 bp and contains four exons separated by three introns. It is located on the human chromosome 4, locus 4q12-q21. There are at least two different types of IL-8 receptors (CXCR1 and CXCR2). The activity of IL-8 is not species-specific. IL-8 affects adhesion of neutrophils to the endothelium and induces transendothelial migration of neutrophils. IL-8 also exhibits *in vitro* chemotactic activity against T-lymphocytes and basophils [35].

Since IL-8 is responsible for induction and maintenance of the inflammatory state, there is a high

probability of a correlation between exacerbations of CB and the serum IL-8 level. W.I. de Boer et al. demonstrated that the IL-8 level in the bronchoalveolar lavage (BAL) was 1.4 times higher compared to the control group, but did not determine a significant correlation between the level of IL-8 in the epithelial tissue and the severity of exacerbation [36]. These findings allow to suppose that the IL-8 level can be a parameter of a local neutrophil response before manifestations of CB exacerbation, which will allow to take preventive measures.

In the experimental model, a relationship between high levels of IL-8 and airway remodeling in diseases associated with chronic inflammation of the lung tissue was revealed, acting directly on smooth muscle cells reducing their length and increasing their sensitivity to inflammation [37]. The work by J. Zhang and C. Bai demonstrated a correlation between the IL-8 level in an exacerbation of chronic obstructive bronchitis and the level of inflammatory markers. In people with COPD without an exacerbation, IL-8 was significantly higher compared to the healthy controls, which may again indirectly indicate a relationship between the level of the cytokine and airway wall remodeling [38].

IL-8 is a promising marker, an increase in which may signal more pronounced airway remodeling in people with persistent COPD. However, this hypothesis is always secondary in the studies mentioned above, and no targeted long-term studies have been carried out on this topic.

## INTERLEUKIN-10

Interleukin-10 (IL-10) is a powerful anti-inflammatory cytokine that reduces inflammation in some disease models [39]. Being an anti-inflammatory cytokine, IL-10 serves to counteract the proinflammatory effects of other cytokines, and thus can strike the balance between pro- and anti-inflammatory systems. IL-10 inhibits expression of cytokines, such as TNFα, IL-1β, and IL-8. It can inhibit expression of adhesion molecules [40]. It has immunoregulatory and pleiotropic effects. It is mainly secreted by macrophages, Th1 and Th2 lymphocytes, dendritic cells, cytotoxic T cells, B lymphocytes, monocytes, and mast cells [41]. It inhibits expression of Th1 cytokines, MHC class II molecules, and co-stimulatory molecules on macrophages. IL-10 increases B-cell survival and proliferation and production of antibodies. IL-10 can also block the activity of NF-κB and is involved in the regulation of the JAK-STAT signaling pathway [42]. Further studies showed that IL-10 mainly inhibits the proinflammatory cytokines TNFα, IL-1β, IL-12, and IFNγ from TLR induced by lipopolysaccharide (LPS) and bacterial production and activates myeloid cells [43].

In terms of pulmonary inflammation, there are currently extensive data on direct involvement of IL-10 in regulation of inflammation in the lungs. According to recent observations, a decreased level of IL-10 was associated with more frequent development of exacerbations in people with CB, and IL-10 levels were significantly lower compared to the healthy controls [44, 45]. In addition, it was demonstrated that serum and sputum levels of IL-10 were higher in healthy, non-smoking patients compared to patients with COPD and healthy smokers [46]. Moreover, the levels of IL-10 in healthy smokers were suppressed in the BAL [47, 48]. Currently, there is some inconsistency among the authors regarding a correlation between IL-10 and other factors that activate inflammation, which is most likely associated with its polymorphism and requires a more detailed and in-depth study [49–51]. Therefore, the IL-10 level may be useful for prognosing the patient's condition in terms of development of bronchopulmonary pathologies and determination of risk groups, as well as for taking more effective preventivemeasures.

## MONOCYTE CHEMOATTRACTANT PROTEIN-1

Monocyte chemoattractant protein-1 (MCP-1, CCL2) appears to be a member of the cytokine group belonging to the CC chemokine family, also known as CCL2. MCP-1 is a monomeric polypeptide with a molecular weight of about 13–15 kDa, depending on the level of glycosylation [52]. CCL2 is mainly secreted by monocytes, macrophages, dendritic cells, epithelial cells, astrocytes, fibroblasts, and endotheliocytes.

The *MCP-1* gene located on the chromosome 17 consists of three exons and two introns; the gene length is 1927 bp [53]. CCL2 is fixed in the plasma membrane of endothelial cells with glycosaminoglycan side chains of proteoglycans. Enhanced production of MCP-1 can occur under the influence of many factors, such as TNF, LPS of bacterial agents, interleukin-1, interferons, platelet growth factor, etc. [54].

Induction of MCP-1 initially attracts monocytes and basophils to the site of inflammation. After deletion of the N-terminal residue, MCP-1 loses its specificity for basophils and becomes an eosinophil chemoattractant. After exposure to MCP-1, basophils and mast cells release their granules into the intercellular space. This effect can also be enhanced by pretreat-

ment with IL-3 or other cytokines [55]. CCL2 is involved in the pathogenesis of several diseases characterized by monocytic infiltrates.

So, in the studies by A. Di Stefano et al., an increase in serum MCP-1 was observed in patients with COPD with an exacerbation compared to patients without COPD [56]. The same trend was demonstrated by S. Traves et al. for the levels of MCP-1 in BAL and sputum: the content of MCP-1 in sputum was elevated in patients with CB compared to the control group and the group of healthy smokers. There was a direct correlation between the level of neutrophils in the sputum and the level of MCP-1 and a negative correlation between the MCP-1 level and FEV1, which suggests that MCP-1 can participate in the inflammatory load during an exacerbation of CB and directly indicates clinical manifestations [57]. This work confirmed the findings of earlier studies on direct involvement of MCP-1 in the inflammatory process and monocyte macrophage infiltration of the bronchiole walls during an exacerbation and without it in patients with CB [58, 59].

## TYPE 1 PLASMINOGEN ACTIVATOR INHIBITOR

Type 1 plasminogen activator inhibitor (PAI-1), also known as an endothelial plasminogen inhibitor, is a serine protease inhibitor that functions as an antagonist of tissue plasminogen activator and inhibits fibrinolysis [ 60]. It is located on the chromosome 7, locus 7q21.3-Q2 in the gene called SERPINE1, in the promoter region of which there is a 5G \ 4G polymorphism [61].

PAI-1 is mainly produced by the endothelium (cells lining the blood vessels). High expression of PAI-1 in cultured endothelial cells suggests that these cells make a significant contribution to the PAI-1 pool. However, *in vitro* studies show that PAI-1 is synthesized by various cells, and its biosynthesis can be caused by growth factors, cytokines, hormones, and other compounds [62].

In pathological conditions, a big amount of PAI-1 is secreted by other tissues: tumor cells, endothelial cells in response to inflammatory cytokines, and other cells activated by inflammation. High plasma PAI-1 levels are constantly detected in patients with severe sepsis, tumor processes, and other acute or chronic inflammatory diseases, such as atherosclerosis. PAI-1 is activated by inflammatory cytokines and, therefore, can be considered as a marker for the ongoing inflammatory process. However, it is very important that no classical elements of the inflammatory response were found in the promoter region of PAI-1, and it is still unclear through what mechanism PAI-1 expression is activated during inflammation [63].

For example, in the analysis of CB and COPD with and without metabolic syndrome (MS) in the ethnic group, it was shown that the polymorphism of alleles can directly predispose to the development of both variants. The 4G \ 4G genotype was more common in the group with MS and in the group with COPD and MS [61], as evidenced by worldwide studies of other ethnic groups [64, 65, 67].

A direct correlation between the clinical data on manifestations of CB and laboratory data was proved in the work by H. Wang et al. Serum PAI-1 levels were significantly increased in patients with COPD, especially in smokers with COPD, and serum PAI-1 levels were associated with parameters of lung function, such as FEV 1 / Pre, FEV 1 / FVC, and CRP [66]. However, neither comorbid COPD nor airflow limitation (from mild to very severe stages) was considered.

According to a similar design, the same results were obtained in the study by B. Waschki et al. The level of PAI-1 increased regardless of the concomitant pathology, and the highest levels of PAI-1 were observed in patients with stage II and III COPD according to Global Initiative for Obstructive Lung Disease (GOLD) [68].

## TISSUE FACTOR

Tissue factor (TF) is a transmembrane protein that is present on the surface of subendothelial tissue and leukocytes and directly involved in the cascade of the coagulation system, both in the external and internal pathways [69]. The tissue factor is a 47 kDa glycoprotein consisting of three domains: the cytoplasmic domain, which is involved in the signaling function of the tissue factor, the hydrophobic transmembrane domain, which passes directly through the membrane, and the extracellular domain, which consists of two fibronectin filaments and a hydrophobic nucleus and has three N-terminal binding sites with carbohydrates. The main function is performed by the last two domains; without the cytoplasmic end, the tissue factor is functional [70].

TF signaling plays a role in the angiogenesis and apoptosis [71]. In the context of coagulation, TF can be found in the pool of circulating TF in the soluble form or bound to the membrane [72, 73].

Monocytes are some of the main sources of TF [74, 75] which is involved in formation of blood clots in pa-

tients with myocardial infarction [76, 77], as well as in other thrombotic diseases [78]. *In vitro* platelet particle generation from differentiated human megakaryocytes showed that platelets can carry both TF and its mRNA [79]. TF is also expressed by neutrophils, triggering thrombin generation and clot formation. Neutrophil activation is necessary for the effect of TF on the cell membrane [80]. Platelets, neutrophils, and, as recently reported, even T-lymphocytes can be an important source of TF in patients [81].

Based on the research data, a hypothesis was put forward on the role of TF not only in coagulation, but also in other pathological processes. So, in a number of studies, it was shown that the level of TF can be increased not only in patients with severe or moderately severe COPD [82], but also in stable CB [83]. Not only did the pool of TF associated with the occurrence of chronic inflammation in the airways increase, but also a decrease in tissue factor pathway inhibitor (TFPI) was recorded, aimed at restraining the procoagulant ability of TF [84]. A direct correlation with other procoagulants and inflammatory markers was also observed [85].

## COMPLEMENT SYSTEM

Complement factors are a part of the immune system, a set of circulating and membrane-bound proteins in human blood, the main function of which is to fight foreign agents [86]. Most of them belong to β-globulins [87]. According to the nomenclature, individual components of the complement system are denoted by the symbols Cl, C2, C3, C4, C5, C6, C7, C8, C9 or capital letters (D, B, P) and are called factors. [88]. There are also regulators of complement activity (RCA), whose main function is to inhibit activation of the complement system and protect cells [89].

There are three main ways to activate the complement system: the classical pathway, the lectin pathway, and the alternative pathway.

Activation of the classical pathway requires the presence of an antigen-antibody pattern. Activation occurs when C1q binds to IgM or IgG in complex with antigens. After that, a cascade of reactions takes place during which the activation of the C3 component occurs [91].

The lectin pathway is homologous to the classical pathway, but instead of C1q, there are opsonin, mannose-binding lectin (MBL), and ficolins. This pathway is activated by binding MBL to mannose residues on the surface of the pathogen, which activates MBL-related serine proteases, MASP-1 and MASP-2, which can then cleave C4 and C2. Their products bind together to form a classical C3 convertase, as in the classical pathway. Further, the pathway continues homologously according to the classical pattern [92].

The alternative pathway is associated with constant hydrolysis of a small amount of the C3 complement molecule due to the presence of a thioester bond in the given molecule. The process is called tickover and its speed is approximately 0.3–1% of C3 molecules per hour. This process has an internal positive loop, due to which, in theory, it should have an avalanche-like nature following support of factors B and D. However, due to factors H and I, this does not happen, as they inhibit this loop by breaking the C3 complex [93].

It is generally accepted that the main site for synthesis of complement system proteins is the liver, however, pulmonary alveolar type 2 epithelial cells synthesize and secrete complement proteins C2, C3, C4, C5 and factor B [94], while human bronchial epithelial cells can generate C3 [95]. Local complement synthesis provides understanding of the interaction between complement factors and lung disease. Inflammatory cytokines, such as IL-6, IL-1, TNFα, and IFNγ, can initiate complement synthesis in cells, such as resident polymorphonuclear leukocytes, epithelial cells, and fibroblasts [96].

Complement anaphylatoxins (C3a, C5a) are powerful inflammatory mediators involved in the exaggerated inflammatory response observed in CB. Recent studies have revealed elevated levels of circulating C3a and C5a in patients with COPD, which indirectly suggests that complement proteins may contribute to the pathogenesis of the disease [97]. Moreover, when assessing the levels of C3 and C4, which account for approximately ⅔ of the total pool of complement proteins, it was found that they were initially lower in patients with chronic obstructive bronchitis; and the more severe the course of the disease, the lower the levels [98, 99].

There is also a large number of studies that suggest that exposure to cigarette smoke leads to chronic activation of the complement system according to the alternative pathway [97, 100, 101]. S. Grumelli et al. obtained data showing that a decrease in CD46 expression correlated with a loss of lung function in COPD, which may help explain the principles of inflammation and excessive complement activation in this group of patients [102]. However, most authors agree that due to the sufficiently large pool of complement proteins and heterogeneity of the studied groups, there is currently no clear understanding of the state

of complement factors in CB, therefore, this topic requires further research [97, 98, 102].

## CONCLUSION

The above-described biochemical markers are involved in the pathological processes in CB. Among these biochemical markers, IL-6 is especially worth noting as a marker that can help in early detection of a disease exacerbation, which allows to start more well-thought treatment. The same can be concluded about MCP-1, however, its evidence base is somewhat smaller and requires more detailed consideration.

These markers are useful not only in the field of scientific knowledge about the pathogenesis of CB, but also in clinical use and as potential targets for targeted therapy for this disease. A more detailed study of these biomarkers may help to construct a model of disease development and develop ways of clinical control and programs for prevention and control of disease sanogenesis.

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