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Biomarkers and their role in the pathogenesis of chronic obstructive pulmonary disease

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Chronic obstructive pulmonary disease (COPD), according to experts WHO, is among the leading causes of morbidity and mortality worldwide. According to WHO, by 2020 COPD will occupy the fifth place in morbidity and third in the structure of mortality. In Europe, annually die from COPD is not less than 200–300 thousand people. Over the past 30 years, the mortality rate of patients with COPD increased 3.3 times in men and 1.5 times in women [1–4].

According consensus GOLD (2015), COPD – a disease that can be prevented and treated, which is characterized by constant airflow limitation is usually progressive and associated with high and chronic inflammatory response in the airways and lungs in action harmful particles or gases. Exacerbations and comorbidities may further burden the course of COPD in some patients [5].

Numerous studies in recent years have shown that the most significant aspect of the problem is to identify predictors of COPD, determine disease severity and prognosis of COPD.

According consensus GOLD (2011–2015), Classification of severity, based on the integrated assessment of severity of COPD patients. It takes into account not only the severity of airflow obstruction (the degree of bronchial obstruction) the results of Spirometric studies, but clinical data about the patient: the number of exacerbations of COPD per year, the severity of clinical symptoms of the results mMRC and COPD Assessment Test (CAT) and the questionnaire Clinical COPD Questionnaire (CCQ). In assessing the risk it is recommended to choose the highest level according to the speed limit airflow GOLD classification or the frequency of exacerbations in history. Thus, integrated assessment of the impact of COPD force on individual patient evaluation combines symptoms of Spirometric classification and assessment of the risk of exacerbations [6].

However, system implementation and integration of these factors needs further improvement. Currently, proved the existence of different phenotypes of COPD: emphysematous – «with frequent exacerbations and emphysema»; bronchitis – «with frequent exacerbations and chronic bronchitis»; no exacerbations and COPD phenotype combined flow and asthma, which indicates that the clinical heterogeneity of the disease [5]. However, in daily practice clear distinction phenotypes spend quite difficult. The decline of forced expiratory volume at 1-second (FEV_1) in COPD is characterized due to local and systemic inflammation and risk factor for morbidity and mortality from cardiovascular disease regardless of smoking status. Indicator FEV_1 is a key reference for selecting not only clinical group in accordance with the recommendations GOLD-2013 and the volume of treatment but also prognostically unfavorable factor increasing the risk of death [7]. And on the disease affect comorbidities that meet more than GOLD classification of severity by measuring lung function [8].

In recent years, actively discussed the role of cytokine status violations in the initiation and progression of inflammation in the broncho-pulmonary system. We cannot fully value ascertainment levels of cytokines

in the chronic inflammatory response in COPD patients with severe course.

Attention to cytokines researchers determined that they provide consistency, harmony and completeness of the immune response. Most cytokines are not only endogenous regulators of immune responses, but the key factors that induce inflammation and acute phase response, may have immunopathological effects on cells and tissues.

High hopes in the medical diagnosis of COPD associated with the analysis are known, and the search for new biomarkers that will assess different aspects of COPD such as pathogenesis, severity, disease prognosis and response to therapy [9].

So the **aim** of the study was to analyze literary sources to determining biomarkers that can characterize disease severity and prognosis of COPD opportunity.

Biomarkers can be defined as in induced sputum and BAL fluid and blood of patients. Thus, during the numerous studies revealed the presence of induced sputum and fluid BAL in patients with COPD high levels of proinflammatory cytokines and other mediators: IL-10, -17A, -17F, -22, TNF-α, IL-8, -17A, -6 and CXCL8, nitric oxide, which further increased during the exacerbation. Increasing the level of IL-8 in the nasal washings significantly associated with increasing pack-years of cigarettes. In addition, IL-8 is positively correlated with the stage of COPD [10–12].

Among the research in recent years, the emphasis is on finding and using biomarkers in blood serum. According to many authors, patients with COPD marked increase in levels of inflammatory markers in peripheral blood, indicating the presence of systemic inflammatory response [13–15]. The main systemic manifestations of COPD include malnutrition and skeletal muscle dysfunction, osteoporosis, anemia, cardiovascular complications, depression, etc. [7]. And systemic inflammatory reaction or systemic inflammation develops from the early stages of the disease when clinical manifestations are minimal or absent altogether. This confirms elevated levels of inflammatory markers in peripheral blood, namely C-reactive protein (CRP), fibrinogen, neutrophil elastase, pro-inflammatory cytokines IL-1β, -6, TNF-α, chemokines IL-8, IFN-α, TGF-β, fibroblast growth factor, epithelial and endothelial growth factor [14, 16]. High-sensitivity CRP is used in combination with the GOLD classification of COPD severity to increase the predictive value of the latter [17].

It was established that the levels of production of IL-2 and -4 in patients with COPD significantly lower data in healthy volunteers, and the level of IL-1β, -6 and -8 exceed these standards. These changes are in the initial phase of inflammation compensatory in nature, but increased levels of proinflammatory cytokines, particularly IL-1β with the progression of COPD is prognostically unfavorable sign of the disease [15, 16, 18]. After testing the load between the groups with severe and very severe COPD there is significant difference in levels of interleukin-6 (IL-6). In addition, lower levels of IL-4 are in the group with severe COPD compared to very severe and moderate COPD [19].

With the same purpose, use some tumor markers (carcino-embryonic antigen (CEA), Cancer antigen 19-9 (CA19-9), Cancer Antigen 125 (CA125), Neuron enolaza (NSE) and cytokeratin 19 pieces (CYFRA21-1)). There is work, which demonstrated an increase in their concentration in the blood, which in turn was associated with elevated levels of inflammatory biomarkers (CRP, erythrocyte sedimentation rate (ESR), white blood cells (WBC)) and the severity of the disease. So inflammation may play a major pathogenic role, linking the increase of tumor markers of severity of COPD [18]. The investigations in the study of the genetic mechanisms of COPD. So scientists had found a link between single-nucleotide polymorphism gene interleukin-4 (polymorphism IL-4-33C/T site) and interleukin-6 (IL-6-572C/G site) and susceptibility to COPD as a theoretical basis for genetic mechanism COPD. Proved that the polymorphism IL-4-33C/T site may not be associated with susceptibility to COPD and polymorphism of the IL-6-572C/G site can be associated with susceptibility to this disease. [21].

In the study the frequency of polymorphic variants of genes ADRB2 (A46G and C79G), NR3C1 (C646G), MDR1 (S3435T) in patients with COPD was found significant difference frequency of genotype GG for gene ADRB2 (C79G) in COPD patients compared with the control group [19]. So genetic predictors involved in the causal pathways. Thus, genetic studies are also necessary for understanding the mechanisms of aggravation and prognosis of COPD [22]. Increased levels of soluble urokinase receptor of activator plasminogens (suPAR) is acute viral and bacterial infections and diseases associated with chronic inflammation. suPAR is a marker of acute inflammation. This is consistent with inflammatory markers like CRP and fibrinogen. suPAR can be used as a predictor of COPD exacerbation and in monitoring response to treatment [23], the same properties predictors of COPD exacerbation is procalcitonin [24].

Another marker of COPD may be IL-17 synthesized Th17-cells, which include CD4+-T-lymphocytes. They are characterized by the secretion of IL-17A, -17F and -22. In addition, IL-17 is synthesized natural killer cells, cytotoxic T-lymphocytes and granulocytes. IL-17 indirectly helping to attract neutrophiles and lymphocytes from the blood of inflammation in the lung by stimulating the secretion of proinflammatory chemokine IL-8, CCL20 and CXCL10 epithelial cells of the airways and alveolar macrophages. The interaction of receptors located on macrophages and dendritic cells with IL-17 stimulates the production of these cells TNF-α [25, 26].

There are many risk factors that mediate not only the origin and progression of bronchial obstruction with subsequent decline in lung function, but cause the manifestation of comorbidis conditions, in turn worsening the clinical picture and prognosis of COPD. The most significant predictors of COPD are cigarette smoke, particulates pollutants, bleomycin or allergens that cause the release of dangerous mediators, such as ATP and/or uric acid that activate inflamasoma NLRP3, which in turn activates caspase-1 release IL-1β. These inflammatory mediators critical that induce the production of IL-6, -23 and chemokines, which promote neutrophiles mobilization and increase the number of Th17-cells in the lungs of increased production of IL-17. This leads to IL-1/-17 dependent lung inflammation, fibrosis and emphysema [23]. It is reported that in smokers with COPD is increased relative Th17-number of lymphocytes in the peripheral blood compared with healthy smokers. In patients with COPD smokers was detected inverse correlation between the number of blood cells Th17- and FEV_1 and the percentage of Th17-lymphocytes and the ratio of FEV_1 to forced vital capacity (FVC). The increase in the relative number of Th17-cells in the blood of smokers led to the presence and severity of airflow limitation. And in smokers with COPD patients levels of IL-17A in the peripheral blood and sputum also increased compared with healthy smokers [26].

It was shown that endogenous predictor of COPD is acetylcholine, which can enhance the level of Th17-cells in systemic inflammation in patients with COPD. So prolonged action β_2-agonists and anticholinergic medications may help control these events [26].

Important is research in the study of immune mechanisms of COPD to improve and clarify the classification of this disease. By studying the immune status of patients with COPD were first identified two immune phenotypes of COPD, immunodeficiency, which is clinically bronchitis and autoimmune (which is more consistent with emphysematous). Based on what has been done clarifying the definition of COPD, a syndrome of obstruction and remodulation bronchi that develops in genetically susceptible individuals after prolonged inhalation of toxins that damage the mucous membrane and cause persistent hyperergic of inflammation, leading to the development of immunodeficiency – bronchitis and/or autoimmune – emphysematous COPD phenotypes, which is an early sign of recurrent bronchitis. Mixed immunological phenotype includes a combination immunodeficiency and autoimmune phenotypes that perhaps more common [4].

According to the literature in the early stages of COPD is most typical for «neutrophil» Subtype cell mediated reaction in the lungs, independent of Th17, which may be non-specific [27, 28]. And after induction of adaptive immune response to auto antigens and infectious antigens, neutrophiles, IgG-antibodies bound their Fcγ-receptors are specifically involved in interactions with antigens, including autologous, damaging their own enzymes [4]. These reactions are determined by genes that determine infiltration of neutrophiles and lung structures cytokines: IL-1β, TNF-α, IL-23, -17, -6, -8, chemokine et al., which in the end determine this neutrophiles mediated hyper reactivity and Th-17 cells are key neutrophiles inflammation. Inducer of inflammatory reactions often appears rhinovirus infection [27, 28].

Dendritic cells and macrophages under the influence of toxins and antigens secrete IL-23, -1β, TGF-β. They stimulate the maturation of cells in T0 Th17, which secrete IL-17 and -22, causing activation of epithelial cells. Last secrete IL-6, -8 and chemokines that stimulate migration of neutrophiles from blood vessels into the tissue. IL-17, which can release as NK and T-CD8+-cells to endothelium activates the expression of adhesion molecules for neutrophiles and secretion of IL-6, -8 and GM-CSF, and IL-22, all of which activate fibroblasts and production of collagen. In addition, IL-17 is involved in the development of autoimmune reactions, especially cells of patients with this cytokine create more than – normal [1].

Increased IL-17 in the lungs of patients with severe COPD may contribute to disease progression and the development of lymphoid follicles via activation of chemokine CXCL12. So given information relating to high value Th17 in the development of many diseases can be considered this cell subpopulation and cytokines produced by it as diagnostic markers of disorders of the immune system in patients with COPD [29]. However, the role of Th17 in the formation of systemic inflammation in patients with COPD remains uncertain until the end, no defined role Th17 – dependent immune responses and the development of COPD in predicting the severity of this disease. Such knowledge is crucial because clinical intervention in the regulation or neutralization of IL-17 is likely to be tested in the near future.

Considerable research interest is in the study of the imbalance of Th1/Th2 and Th17-cells, which is associated with the occurrence of COPD [30]. It was also shown that there is an exacerbation of COPD imbalance of Th17/Treg (regulatory T-cells) in the direction of Th17-cell-type, while with stable COPD balance shifted toward the anti-inflammatory response. Also imbalance of these cells is strongly associated with worsening of lung function and severity of COPD [31, 32]. Smoking cigarettes can contribute to this imbalance, influencing the polarization and the survival Th17/Tregs by regulation of muscarinic receptor MR3 and MR5 [33].

Conclusions

At the present stage of science accumulated numerous data on the role of inflammatory cells (neutrophiles, macrophages, T-cells), inflammatory mediators

and cytokines in the pathogenesis of COPD. However, these data indicate that in the literature there is no single point of view on the direction of changes in cytokine production in patients with COPD, as there is no single point of view on specific inflammatory markers or combinations in COPD.

Evaluation of cytokines in various biological materials (serum, whole blood, culture supernatants and others) must occupy a central place in modern methods of immune-diagnostics that will evaluate various aspects of COPD such as pathogenesis, severity, disease prognosis and response to therapy.

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БІОМАРКЕРИ ТА ЇХ МІСЦЕ У ПАТОГЕНЕЗІ ХРОНІЧНОГО ОБСТРУКТИВНОГО ЗАХВОРЮВАННЯ ЛЕГЕНЬ

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Резюме

Мета – *проаналізувати літературні джерела інформації на предмет визначення біомаркерів, що можуть характеризувати тяжкість захворювання та можливість прогнозування перебігу хронічного обструктивного захворювання легень (ХОЗЛ).*

Результати. *За даними літератури, при проведенні численних досліджень виявлено наявність у індукованому мокротинні і рідині БАЛ у хворих на ХОЗЛ високих рівнів прозапальних цитокінів та інших медіаторів: IL-10, -17A, -17F, -22, TNF-α, IL-8, -17A, -6 і CXCL8, оксиду азоту, які ще більше підвищуються в період загострення. В периферійній крові хворих на ХОЗЛ відзначається підвищення рівнів маркерів запалення, що свідчить про наявність системної запальної реакції. Встановлено, що рівні продукції IL-2 та -4 у хворих на ХОЗЛ значно нижчі, ніж такі у здорових донорів, а рівні IL-1β, -6 та -8 перевищують дані норми. Ще одним маркером ХОЗЛ може служити IL-17, що синтезується Th17-клітинами, до яких відносять CD4+-Т-лімфоцити. За даними літератури, на початкових етапах для ХОЗЛ найбільш характерний «нейтрофільний» субтип клітинно-опосередкованої реакції в легенях, залежний від Th17. Також було доведено, що при загостренні ХОЗЛ спостерігається дисбаланс Th17/Treg (Т-регуляторних клітин) у бік клітин Th17-типу, що тісно пов'язаний з погіршенням легеневої функції та тяжкістю ХОЗЛ.*

Висновки. *На сучасному етапі розвитку науки накопичені численні дані щодо ролі клітин запалення (нейтрофілів, макрофагів, Т-лімфоцитів), прозапальних медіаторів і цитокінів у патогенезі ХОЗЛ. Оцінка рівня цитокінів в різних біологічних матеріалах (сироватці, цільній крові, культуральних супернатантах та ін.) повинна зайняти центральне місце серед сучасних методів імунодіагностики, які дають змогу оцінити різні аспекти ХОЗЛ, такі як патогенез, тяжкість, прогноз хвороби і відповідь на терапію.*

Ключові слова: *хронічне обструктивне захворювання легень, біомаркери, IL-17.*

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БИОМАРКЕРЫ И ИХ МЕСТО В ПАТОГЕНЕЗЕ ХРОНИЧЕСКОГО ОБСТРУКТИВНОГО ЗАБОЛЕВАНИЯ ЛЕГКИХ

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Резюме

Цель – *проанализировать литературные источники информации на предмет определения биомаркеров, которые могут характеризовать тяжесть заболевания и возможность прогнозирования течения хронического обструктивного заболевания легких (ХОЗЛ).*

Результаты. *По данным литературы, при проведении многочисленных исследований выявлено наличие в индуцированной мокроте и жидкости БАЛ у больных ХОЗЛ высоких уровней провоспалительных цитокинов и других медиаторов: IL-10, -17A, -17F, -22, TNF-α, IL-8, -17A, -6 и CXCL8, оксида азота, которые еще больше увеличиваются в период обострения. В периферической крови у больных ХОЗЛ отмечается повышение уровней маркеров воспаления, что свидетельствует о наличии системной воспалительной реакции. Установлено, что уровни продукции IL-2 и -4 у больных ХОЗЛ значительно ниже таковых у здоровых доноров, а уровни IL-1β, -6 и -4 превышают данные нормы. Еще одним маркером ХОЗЛ может служить IL-17, синтезирующийся Th17-клетками, к которым относятся CD4+-Т-лимфоциты. По данным литературы, на начальных этапах для ХОЗЛ наиболее характерен «нейтрофильный» субтип клеточно-опосредованной реакции в легких, зависящий от Th17. Также было доказано, что при обострении ХОЗЛ наблюдается дисбаланс Th17 / Treg (Т-регуляторных клеток) в сторону клеток Th17-типа, который тесно связан с ухудшением легочной функции и тяжестью ХОЗЛ.*

Выводы. *На современном этапе развития науки накоплены многочисленные данные о роли клеток воспаления (нейтрофилов, макрофагов, Т-лимфоцитов), провоспалительных медиаторов и цитокинов в патогенезе ХОЗЛ. Оценка уровня цитокинов в различных биологических материалах (сыворотке, цельной крови, культуральных супернатантах и др.) должна занять центральное место среди современных методов иммунодиагностики, которые позволят оценить различные аспекты ХОЗЛ, такие как патогенез, тяжесть, прогноз болезни и ответ на терапию.*

Ключевые слова: *хроническое обструктивное заболевание легких, биомаркеры, IL-17.*

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