Respiratory tract microbiome as an important prognostic marker of chronic pulmonary diseases

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Abstract

Chronic obstructive pulmonary diseases (COPD, bronchiectasis) are increasing in prevalence worldwide. The main task in the treatment of this diseases is to control the symptoms of the disease, prevent exacerbations and stop the progression. Effective treatment remains a problematic issue, given the pathogenetic features of these nosologies. An in-depth understanding of the effects of lung microbiome in pathology can shed light on these insufficiently studied issues, because in the human lungs is concentrated a huge number of microorganisms, which have a huge impact on body health and the development of diseases. Each person is characterized by individually stable genotypes of microbial representatives. Quantitative and qualitative changes of these microbiocenoses can have a significant impact on the development and outcomes of lung diseases. Thus, *Pseudomonas-* and *Haemophilus*-dominant variants of the lung microbiome are associated with severe pulmonary pathology and frequent exacerbations. This review highlights the main studies of lung microbiome in pathology and possible prospects for its regulation for therapeutic purposes.

Key words: chronic pulmonary diseases, respiratory microbiome, COPD phenotypes.

Microbiome is a complex of genetic material of all microorganisms in the environment [1]. Whereas the microbiota is an ecological community of symbiotic and pathogenic microorganisms that coexist in a specific environment (niche). The main purpose of studying the microbiome is to understand that the human body is the host for a huge number of microorganisms that interact with it, as well as interact with each other and have a huge impact on both body health and the development of its diseases [2,3]. The deepening understanding of the role of the microbial world in the last decade has led to the emergence of new terms, for example, within the framework of "pharmacogenomics" the definition of "pharmacomicrobionomics" is proposed. It is clear that the aim of this research is the interaction between pharmacological intervention and the effects of such effects on the microbiome and the course of the disease or on human health generally.

According to the results of pharmacotherapy, a serious attitude to the microbiota of the human body is required, taking into account the genetic individual characteristics and polymorphism of each individual. Moreover, it is necessary to take

into account some differences between the variants of microtopes in their localization in different organs - intestine, lungs, skin, genitals.

The lung microbiome of a healthy person is characterized by inconsistency and depends on several main factors: 1) microbial immigration (movement of microorganisms from inhaled air, through microaspiration and directly from the mucous membrane); 2) the speed of movement of the cilia of the bronchial epithelium and the activity of the local immune system; 3) weather conditions of human habitation, which contribute to the development and growth of individual strains [4]. Airways diseases disrupt the morphology and structure of the lung parenchyma, thus changing the local conditions for the development and growth of microbial populations. In chronic lung diseases (COPD, bronchiectasis) due to violations of the anatomical and morphological features of the respiratory tract and reduced mucociliary clearance (MCC), favorable conditions may be observed for rapid colonization by various pathogens and the development of chronic infection [5].

Bronchiectasis is a fairly common pathology of the lower respiratory tract, occurring in Europe in the range from 67 to 566 cases per 100 thousand population and more than 1200 per 100 thousand inhabitants of China, which causes significant damage to the economy of these countries [6].

Periodic episodes of exacerbations of the disease have a negative impact on the quality of patients' life and their financial costs, cause progressive damage to the lung parenchyma and a high risk of death [7,8]. The quantitative and qualitative composition of microorganisms of the respiratory tract plays an important role in this. For example, a pathogen such as *Pseudomonas aeruginosa*, more than any other member of the bacterial flora is associated with rapid progression, unfavorable prognosis of bronchiectasis [9,10]. Thanks to modern molecular technologies used to study pulmonary microbial populations, it is now possible to understand the role of infectious agents in the pathophysiology of chronic respiratory diseases. It is the pulmonary microbiocenosis that can form the phenotype/endotype of the disease, susceptibility and sensitivity to pharmacotherapy [11,12].

Microbiological studies in bronhciectasis have revealed a complex of different strains of microorganisms that are highly individual for each patient [13,14]. Quite an interesting study by Woo et al. [15] for 16 years demonstrated clear microbiome stability in each patient throughout the observation period. Two completely different dominant microbiomes, *Pseudomonas*-associated and *Haemophilus*-associated, were identified in patients who maintained this profile for most of the time, despite the use of antibiotics [15]. Such results are in complete agreement with the results of crops in which *P. aeruginosa* or *H. Influenza* often persist for years on the background of appropriate pharmacotherapy [16].

Exacerbation of chronic lung disease can be caused by a number of bacteria, viruses and other environmental factors. It is known that the bacterial "load" in the lungs is important in the processes of local inflammation and forms the response to therapy [17,18]. Changes in the microbiome during exacerbations of bronchiectasis are quite heterogeneous. In some studies, the changes were quite minimal, while in

others - there were significant differences with the emergence of new species of microorganisms [14]. In the general conclusion made by Cox et al., there was no significant increase in bacterial load compared to baseline, and no other qualitative changes in the parameters of the microbiome during exacerbations. This does not prove that the microbiome is not involved in exacerbations of disease, but different variants of exacerbations may be the result of certain identified subtypes. In addition, no differences in bacterial load were detected either during exacerbation, or after treatment, or after remission.

In a double-blind, placebo-controlled, randomized BLESS study (Bronchiectasis and Low Dose Erythromycin Study), low doses of erythromycin (400 mg twice daily) were administered to patients with a stable course of disease for 48 weeks [19]. As a result, there was a significant reduction in exacerbations compared with placebo. After analysis of the patient's microbiomes, it was found that *Haemophilus*-dominant microbiome was associated with a small number of exacerbations, while patients with *Pseudomonas* or *Veillonella* microbiome profiles predominated among exacerbations [20]. It is known that patients with *Pseudomonas*-associated type have a worse prognosis, frequent exacerbations, rapid decline in lung function, increased sputum production and higher requirement for administration of antibiotics [21,22,23]. In the same study, *Pseudomonas* and *Haemophilus*-dominant microbiomes were associated with a significant decline of lungs function compared to other microbiome profiles (FEV1 - 56.8%, 69.9% and 73.1%, respectively) [20].

Based on the BLESS cohort of patients, the microbiome was also compared with the severity of the inflammatory process (IL-1β in sputum, IL-8, matrix metalloproteinases (MMPs) and plasma C-reactive protein (CRP)). Multigenic microbiome was negatively associated with inflammatory markers, including CRP, sputum IL-1β, and IL-8. A completely opposite picture was found in patients with *Pseudomonas* and *Haemophilus*-dominant types - the level of markers of inflammation in patients with bronchiectasis was significantly higher compared to other variants [20,24]. Stratification of patients according to microbiome type also demonstrated the association of *Haemophilus*-dominant microbiome with significantly higher levels of metalloproteinases (MMP2 and MMP8) compared to *Pseudomonas* microbiome.

Another pulmonary disease, which is characterized by a classic example of the interaction of genes, environmental factors and human microbiocenosis may be COPD. The rapid increase in the incidence of COPD, high mortality (up to 10%) create significant socio-economic losses in developed countries. Among the pathogenetic components of COPD, along with the aggressive effects of nicotine and stimulation of the cholinergic system, the leading role is played by chronic inflammation of the respiratory tract, MCC disorders and colonization by pathogens. In 2018, a group of international scientists identified a potential marker of exacerbation of COPD with a high mortality rate [25]. Not surprisingly, there was a prognostic imbalance between certain representatives of microorganisms - *Veillonella*, a representative of the residual microflora of the oral cavity, and pathogenic *Staphylococcus*. *Veillonella* (+) COPD phenotypes were characterized by a positive disease course (reduced exacerbations,

lower frequency of hospitalizations) compared with *Veillonella* (-) phenotypes. In the absence of the specified representative in a sputum of patients increase of one-year mortality of patients in 13 times was noted.   Conversely, the presence of *Staphylococcus* (+) in patients with COPD resulted in a 7-fold increase in the risk of one-year mortality and an increase in hospital stay.

Thus, the search for associations between the lung microbiome and the degree of progression of chronic lung disease requires further study and research. Clarification of the spectrum of microbial associations of the respiratory tract in the context of exacerbations of chronic lung pathology should be considered a necessary reality today. At the same time, the recommendations of empirical antibiotic therapy and the introduction of international protocols with emphasis on broad-spectrum drugs virtually eliminate the individual characteristics of each patient, which certainly cannot be considered appropriate and safe.

References

1.Watson R.L., de   Koff E.M., Bogaert D. Characterising   the   respiratory microbiome. Eur Respir J 2019; 53: 1801711.

2.Han M.K., Zhou Y., Murray S. et al. Lung microbiome and disease progression in idiopathic pulmonary fibrosis: an analysis of the COMET study. Lancet Respir Med 2014; 2: 548–556.

3.Faner R., Sibila O., Agustí A. et al. The microbiome in respiratory medicine: current challenges and future perspectives. Eur Respir J 2017; 49: 1602086.

4.Dickson R.P., Huffnagle G.B. The lung microbiome: new principles for respiratory bacteriology in health and disease. PLoS Pathog 2015; 11: e1004923.

5.Flume PA, Chalmers JD, Olivier KN. Advances   in   bronchiectasis: endotyping, genetics, microbiome, and disease heterogeneity. Lancet 2018; 392: 880–890.

6.Chandrasekaran R, Mac Aogáin M, Chalmers JD, et al. Geographic variation in the aetiology, epidemiology and microbiology of bronchiectasis. BMC Pulm Med 2018; 18: 83.

7.Aksamit T, De Soyza A, Bandel T-J, et al. RESPIRE 2: a phase III placebo-controlled randomised trial of ciprofloxacin dry powder for inhalation in non-cystic fibrosis bronchiectasis. Eur Respir J 2018; 51: 1702053.

8.De Soyza A, Aksamit T, Bandel T-J, et al. RESPIRE 1: a phase III placebo-controlled randomised trial of ciprofloxacin dry powder for inhalation in non-cystic fibrosis bronchiectasis. Eur Respir J 2018; 51: 1702052.

9.Chotirmall SH, Chalmers JD. RESPIRE: breathing new life into bronchiectasis. Eur Respir J 2018; 51: 1702444.

10.Kelly C, Evans DJ, Chalmers JD, et al. Macrolide antibiotics for non-cystic fibrosis bronchiectasis. Cochrane Database Syst Rev 2016; 2016: CD012406.

11.Chalmers JD, Chotirmall SH. Bronchiectasis: new   therapies   and   new perspectives. Lancet Respir Med 2018; 6: 715–726.

12.Boaventura R, Sibila O, Agusti A, et al. Treatable traits in bronchiectasis. Eur Respir J 2018; 52: 1801269.

13.Rogers GB, Bruce KD, Martin ML, et al.The effect of long-term macrolide treatment on respiratory microbiota composition in non-cystic fibrosis bronchiectasis: an analysis from the randomised, double-blind, placebo-controlled BLESS trial. Lancet Respir Med 2014; 2: 988–996.

14.Cox MJ, Turek EM, Hennessy C, et al. Longitudinal assessment of sputum microbiome by sequencing of the 16S rRNA gene in non-cystic fibrosis bronchiectasis patients. PLoS One 2017; 12: e0170622.

15.Woo TE, Lim R, Heirali AA, et al. A longitudinal characterization of the non-cystic fibrosis bronchiectasis airway microbiome. Sci Rep 2019; 9: 6871.

16.Woo TE, Duong J, Jervis NM, et al. Virulence adaptations of *Pseudomonas aeruginosa* isolated from patients with non-cystic fibrosis bronchiectasis. Microbiology 2016; 162: 2126–2135.

17.Sibila O, Laserna E, Shoemark A, et al. Airway bacterial load and inhaled antibiotic response in bronchiectasis. Am J Respir Crit Care Med 2019; 200: 33–41.

18.Chalmers JD, Smith MP, McHugh BJ, et al. Short- and long-term antibiotic treatment reduces airway and systemic inflammation in non-cystic fibrosis bronchiectasis. Am J Respir Crit Care Med 2012; 186: 657–665.

19.Serisier DJ, Martin ML, McGuckin MA, et al.Effect of long-term, low-dose erythromycin on pulmonary exacerbations among patients with non-cystic fibrosis bronchiectasis: the BLESS randomized controlled trial. JAMA 2013; 309: 1260–1267.

20. Rogers GB, Zain NMM, Bruce KD, et al.A novel microbiota stratification system predicts future exacerbations in bronchiectasis. Ann Am Thorac Soc 2014; 11: 496–503.

21.Araújo D, Shteinberg M, Aliberti S, et al. The independent contribution of *Pseudomonas aeruginosa* infection to long-term clinical outcomes in bronchiectasis. Eur Respir J 2018; 51: 1701953.

22.Vallières E, Tumelty K, Tunney MM, et al. Efficacy of *Pseudomonas aeruginosa* eradication regimens in bronchiectasis. Eur Respir J 2017; 49: 1600851.

23.Chalmers JD, Aliberti S, Filonenko A, et al. Characterization of the "frequent exacerbator phenotype" in bronchiectasis. Am J Respir Crit Care Med 2018; 197: 1410–1420.

24.Taylor SL, Rogers GB, Chen AC-H, et al. Matrix metalloproteinases vary with airway microbiota composition and lung function in non-cystic fibrosis bronchiectasis. Ann Am Thorac Soc 2015; 12: 701–707.

25.Leitao Filho FS, Alotaibi NM, Ngan D et al. Sputum Microbiome is Associated With 1-Year Mortality Following COPD Hospitalizations. AJRCCM Articles in Press. Published on 30-October-2018 as 10.1164/rccm.201806-1135OC.