

Research Article

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Structure of Respiratory Flora in Chronic Respiratory Diseases

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Abstract

Attention has been paid to the relationship between respiratory flora and respiratory diseases. The respiratory tract is an important channel for the exchange of gas between the human body and the external environment, and it is also a place for various microorganisms to settle and multiply. The microbial communities in the respiratory tract constitute a complex ecosystem, including bacteria, fungi, and viruses. These microorganisms play an important role in maintaining respiratory immune balance and function. Recent studies have shown that the imbalance of respiratory flora is closely related to the occurrence and development of a variety of respiratory diseases. For example, respiratory diseases such as cystic fibrosis, asthma, chronic obstructive pulmonary disease, and lung cancer are associated with an increase or decrease in specific microorganisms. Not only that, changes in the respiratory flora may also affect the host's immune response and exacerbate the pathological process of the disease. Therefore, the in-depth study of the interaction mechanism between respiratory flora and respiratory diseases is of great significance for the prevention and treatment of respiratory diseases. Future studies should further explore the specific mechanism of action of respiratory microbiome in the occurrence of diseases, and search for regulatory strategies targeting respiratory microbiome, so as to provide new ideas and methods for individualized treatment of respiratory diseases.

Keywords: Respiratory Flora; Microorganism; Cystic Fibrosis Asthma; COPD

Introduction

The human body is a complex organism, and there are many microbial communities in the healthy human body that grow and reproduce, and the internal environment of the human body constitutes a harmonious whole that depends on each other. The human body provides a suitable living environment for the growth of microorganisms and provides corresponding nutrients, and the type and number of microorganisms play a crucial role in resisting the invasion of external pathogens and maintaining the stability of the internal environment. The interaction between the microbial communities colonized in the skin, respiratory tract and digestive tract of the human body constitutes a relatively stable internal environment of the body. Previous studies have suggested that specific diseases are determined by specific pathogenic microorganisms, but the current view is that diseases are often the result of the interaction between the organism's biodiversity and the organism. Although there are few studies on the microbial structure of the respiratory tract, the changes of the bacterial structure of the respiratory tract are closely related to the occurrence and development of respiratory diseases. Many studies have shown that changes in respiratory microecology are associated with a variety of diseases, such as respiratory infection, asthma, pulmonary cystic fibrosis, chronic obstructive pulmonary disease, etc., in health and disease states, the type and number of respiratory microorganisms in different parts are also different. With the development of molecular biology technology, new progress has been made in the structure of respiratory tract flora and the change of flora structure in disease state. In this paper, the new technology of studying the structure of respiratory tract microflora, the characteristics of respiratory tract microflora in healthy people, the changes of microflora in the condition of respiratory system disease and the methods of treatment of respiratory system disease are summarized. This study can improve the understanding of respiratory microbiome and provide some theoretical basis for the diagnosis, treatment and drug development of respiratory diseases.

Methods for the Study of Respiratory Tract Flora

In the past, the identification and analysis of respiratory microorganisms often took specific bacteria as the research object and used specific culture conditions and methods to identify, which could not analyze multiple microbial flora at the same time, and could not accurately achieve the experimental purpose. With the rapid development of molecular biology technology and the wide application of sequencing technology, the research on respiratory tract microflora has reached a new level, making it possible to identify and analyze the complete microbial flora of respiratory tract, and establishing a new direction of microbiome research [1]. Currently, 16sRNA sequencing and metagenomic sequencing are commonly used in the study of microbial flora. 16sRNA sequencing is a gene for detecting microbial genome, which is highly conservative and specific, widely used and less expensive. 16sRNA is a subunit of ribosomal RNA, and 16sDNA is the gene that encodes this subunit, which is present in all bacterial chromosomes. The 16sRNA gene consists of about 1540 nucleotides, which is suitable in length, structurally intact, and highly conserved. By using the second-generation sequencing technology, a pair of primers were designed to amplify the 16sRNA gene as a template, and the resulting gene fragment was compared with the established gene bank [2], the species and diversity characteristics of the microbial flora to be tested could be analyzed and the in-depth analysis of the microbial flora could be completed. Metagenome is the detection of the entire gene sequence of microbial flora, which can not only identify the species, but also study the function and metabolism of the microbiome. The advantage of gene sequencing analysis of microbial flora is that it is no longer limited to the specificity required by traditional single species bacteria, and all microorganisms can be identified at the same time, and more abundant biological information can be found from it [3].

Currently, bronchoalveolar lavage fluid (BALF) and protected specimen brushing (PSB) are commonly used to study respiratory flora. Respiratory tract specimens are easily contami-

nated by upper respiratory tract microorganisms in the collection process, but many studies have shown that such pollution has little impact on the collection process, and there is no difference in the microbial flora of specimens collected by different ways [4-7]. Many patients with chronic obstructive lung disease (COPD) and cystic fibrosis (CF) had their samples taken from sputum, but the results showed that the biologic characteristics of the microbiome were largely unaffected by the pollution of the upper respiratory tract, The clinical changes of microbiota in different disease states are still preserved [8-11].

Structure of Respiratory Tract Flora in Healthy Human

The human respiratory tract consists of the upper respiratory tract and the lower respiratory tract, the upper respiratory tract includes the nasal cavity, the pharynx, and the larynx, and the lower respiratory tract consists of the trachea, the main bronchus, and the bronchus at all levels of the lung. As a channel connecting with the outside world, there are many kinds of microorganisms on the respiratory mucosa. For a long time, the lower respiratory tract was generally considered sterile [12]. In 2010, Hilty of the National Heart and Lung Institute of Imperial College London conducted 16sRNA sequencing on lung bronchus samples and found that various microbial communities existed on the lungs [13]. Later, Charlson et al. from the University of Pennsylvania School of Medicine used Q-PCR, DNA barcoding and 454 sequencing technology to systematically elaborate the distribution and diversity of microecology at the vertical level of the entire respiratory tract for the first time [14]. He analyzed the samples of the upper and lower respiratory tracts respectively, and found that the types of microorganisms in the upper and lower respiratory tracts were basically the same, only the number was different, showing a high degree of homology.

With the development of sequencing technology, Blainey et al. confirmed that the respiratory tract of healthy people was mainly colonized by 5 bacteria phyla: Firmicutes (53.139%), Bacteroides (15.724%), Proteobacteria (12.482%), actinobacteria (6.672%) and Clostridium (5.271%). It can be seen that Firmicutes and Bacteroides are the dominant bacteria in respira-

tory tract flora [15].

In the upper respiratory tract, the flora structure of nose, nasopharynx, oropharynx and oral cavity were also significantly different. The nasal flora is rich in actinobacteria (corynebacterium and propionibacterium), Firmicutes (Staphylococcus in adults and Streptococcus in children), and a small number of bacteroidetes. From shortly after birth, the human nasopharyngeal flora changes. The nasopharynx is initially rich in Moraxella, corynebacterium, Streptococcus, or Glucococcus, which can be acquired during the perinatal period (gluconococcus, Corynebacterium) or from the mother's vagina (Streptococcus or Staphylococcus) [16,17]. In addition, the feeding pattern of the newborn plays an important role in the establishment of nasopharyngeal microorganisms. The adult nasopharyngeal flora was basically the same as that of children except for the absence of Moraxella. The oropharyngeal flora of adults is highly diverse, and research results show that streptococcus, Neisseria, Haemophilus influenzae and possibly gram-negative anaerobic symbiotic bacteria exist in the pharynx of healthy adults. Human oral flora is affected by many factors, but its composition is constant, including Staphylococcus, Veillonococcus, Clostridium and so on.

The respiratory tract has been in the external environment for a long time, forming a unique ecological gradient change from nasal cavity to alveoli. In 2014, Dickson proposed a modified island model of lung ecogeography, in which microbial migration, microbial elimination and microbial relative multiplication rate are the three main factors for judging microbial composition [18]. The lung environment of healthy people is not suitable for microbial growth, so the composition of lung microorganisms is mainly determined by the migration and elimination rate of upper respiratory tract bacteria. Respiratory tract and lung microbial growth conditions include pH value, oxygen partial pressure, temperature, relative alveolar ventilation, epithelial structure, number and function of immune cells, etc., which determine the growth and reproduction rate of microorganisms [19].

Under normal circumstances, the respiratory tract flora is balanced in type and quantity to prevent the invasion of foreign microorganisms; When the body is damaged and the resis-

tance is reduced, the structure and number of respiratory tract flora will also change, affecting the normal physiological function of the body. Therefore, respiratory flora is closely related to human health.

Structure of Respiratory Flora in Chronic Respiratory Diseases

Respiratory Tract Flora Structure of Cystic Fibrosis (CF)

Pulmonary cystic fibrosis is a multi-organ genetic disease characterized by exocrine gland dysfunction, mucous gland hyperplasia, and viscous secretion. Clinically, there are a series of symptoms caused by the blockage of the glandular ducts of the airways, lungs, pancreas, intestine, biliary tract, vas deferens and so on, especially the respiratory system damage is the most serious. Pulmonary cystic fibrosis is an autosomal recessive genetic disease caused by the mutation of CF gene located on chromosome 7. Studies have found that the occurrence of CF is related to bacterial infection caused by mutation of the transmembrane regulatory factor gene CFTR. Lung and digestive tract are the main organs involved, and thick secretions blocking bronchus and causing bacterial infection are the pathological basis of respiratory system diseases.

Under normal circumstances, the identification of pulmonary cystic fibrosis adopts the method of in vitro culture of the patient's sputum. At present, the known pathogen is *Pseudomonas aeruginosa*, *Haemophilus influenzae* and *Staphylococcus aureus*, etc. [20]. In recent years, with the development and wide application of 16sRNA sequencing technology, such as end-restricted fragment length polymorphism analysis [21], pyrosequencing technology, and microarray hybridization technology [22-24], the structure of respiratory flora in patients with pulmonary cystic fibrosis has also been further studied. Blainey et al. found that the diversity of respiratory flora in patients with pulmonary cystic fibrosis was significantly reduced compared with healthy people, and the severity of the disease was related to the reduction of microbial diversity [4]. The structure of respiratory flora in patients with pulmonary cystic fibrosis is complex, and compared with healthy people, actinomycetes have greater changes, and the

proportion of other bacteria is: Firmicutes (52.22%), actinomycetes (24.80%), Proteobacteria (17.36%), Bacterioides (3.52%), and Fusobacteria (0.22%). The structure of lung flora is destroyed and the flora is dysfunctional, which may be one of the causes of pulmonary cystic fibrosis. Yang Chang et al. from Zhongshan Hospital in Hubei Province applied 16sRNA sequencing technology to study the structural changes of respiratory tract flora in adult CF patients within one year, and concluded that the long-term colonization of respiratory tract flora in adult CF patients was relatively stable and not susceptible to respiratory tract infections and antibiotics [25].

Structure of Respiratory Tract Flora in Chronic Obstructive Lung Disease (COPD)

Chronic obstructive lung disease (COPD) is a type of chronic bronchitis and emphysema with obstructive air flow. It is characterized by airflow obstruction and is accompanied by an inflammatory response of the lungs to harmful gases and particles. COPD mainly affects the lungs, but it also affects other organs throughout the body. COPD is a slowly progressing respiratory disease with a large number of patients and a low cure rate. The long-term slow course of the disease has a serious impact on the quality of life of patients. The risk factors of COPD are mainly dust, air pollution, smoking and other external factors, but also include genetics, airway reactivity and other personal factors.

Studies on microbial flora of COPD have traditionally been carried out by specific cultures of specific pathogens, such as *Pseudomonas aeruginosa* and *Haemophilus haemophilus*, etc. [26], so it is not clear about all respiratory flora of COPD patients. In the latest study, for the dominant flora in the lower respiratory tract of COPD patients, some scholars reported Proteobacteria, while others concluded that it was Firmicutes and actinobacteria. Pragman conducted sampling and sequencing analysis of alveolar lavage fluid in moderate and severe COPD patients, and found Proteobacteria. Firmicutes and actinomycetes are abundant in the respiratory tract of patients [27], while Cabrera-Rubio et al. showed that the main bacteria groups in the respiratory tract of patients with COPD were *Streptococcus*, *Prevobacillus*, *Moraxella*, etc. [28]. Pragman et al. also found that the types of respiratory

microflora in COPD patients were higher than those in the control group. However, Erb-Downword et al. found that patients with severe COPD had fewer types of respiratory microorganisms than those with mild COPD and the control group [29]. Zakharkina et al. studied healthy people and COPD patients, and found that there were common microbial flora in the respiratory tract of COPD patients and healthy people, such as *Prevotella*, *Sphingomonas*, and *Sphingomonas*. *Pseudomonas* et al. [30]. Other studies have shown that the main flora obtained from sampling in different parts of the respiratory tract are also different [31,32]. Although the results of studies on the respiratory microbiota of COPD patients are different, they all show that the respiratory microbiota of COPD patients and healthy people is different, which provides a new way and method for the treatment of COPD.

In recent years, studies on COPD and gut microbiota have also been carried out. The stability of intestinal microbial structure is also closely related to human health. Once the intestinal microbial flora environment is disturbed, it will cause the release of endotoxins, inflammatory mediators, etc., which also plays a certain role in the occurrence of COPD [33]. Therefore, the study of COPD intestinal microecology will also provide support for the prevention and control of COPD.

Respiratory Microbiota Structure in Asthma

Asthma, also known as bronchial asthma, is a chronic airway inflammation involving a variety of cells and cell components, often causing increased airway reactivity, resulting in repeated episodes of wheezing, shortness of breath, chest tightness and cough. There are many causes of asthma, from the role of genetic factors, but also the inhalation of allergens in the external environment. As the incidence of asthma is increasing year by year, various kinds of research on asthma are gradually increasing. Epidemiological studies have shown that microbial exposure in early childhood is closely related to the incidence of asthma [34]. Studies have shown that children living on farms in early childhood are less likely to develop asthma than the control population [35]. Previous studies have also focused on the relationship between intestinal flora and asthma [36-39]. With the continuous development of biological technology, the level of asthma research is getting deep-

er and deeper. In recent years, studies on the structure of respiratory microflora in patients with asthma have been carried out. Hilty et al. [40] discovered the existence of respiratory microflora. When studying the respiratory microflora of asthma patients and healthy people, they used bronchoscope cell brush to sample and sequence the lungs and found that the structure of respiratory microflora of patients with asthma was different from that of healthy people, among which *Proteobacteria*, such as *Hemophilus* and *Moraxella*, increased significantly. At the same time, Huang et al.'s study on asthmatic patients showed that the bacterial flora structure in the respiratory tract of asthmatic patients changed, and the types and quantity of bacteria were significantly higher than that of healthy people, the number of pathogenic bacteria increased while the beneficial bacteria decreased, and the homeostasis structure of respiratory microorganisms was destroyed [41,42]. Therefore, the structural imbalance of respiratory tract flora and the reduction of bacterial diversity have a great impact on the occurrence of asthma.

Respiratory Microbiota Structure in Lung Cancer

Lung cancer is one of the most harmful malignant tumors to human life and health. In recent years, the incidence and mortality of lung cancer have increased significantly [43]. The most important risk factor for lung cancer is smoking, among which nitrosamines and multi-chain aromatic hydrocarbons [44] and other substances have strong carcinogenicity. A large number of data show that there is a close relationship between a large number of smoking and the occurrence of lung cancer. In addition, genetics, occupational environment, lung infection, etc. are important causes of lung cancer.

Rybojad et al. studied the lower respiratory tract flora of lung cancer and found that *actinomyces* and *peptostreptococcus* were the most abundant flora in the lower respiratory tract of patients [45]. Later, it was also reported that the microflora structure of lower respiratory tract of lung cancer patients was different from that of control group.

At present, the study on the relationship between the structure of respiratory tract microflora and lung cancer is still in progress. The influence of respiratory tract microflora in the occurrence and development of lung cancer cannot be ig-

nored, and respiratory tract microflora has become an important direction of lung cancer research.

The microflora change characteristics of different chronic respiratory diseases are shown in the table 1.

Table 1: Microflora changes in chronic respiratory diseases

Chronic respiratory diseases	Structure changes of respiratory flora
Cystic fibrosis	Actinomycetes changed greatly, followed by Firmicutes, actinomycetes), Proteobacteria, Bacterioides, and Fusobacteria.
Chronic obstructive lung disease	Proteobacteria, Firmicutes and actinobacteria are abundant in the respiratory tract of patients (Pragman et al).The main bacteria groups are Streptococcus, Prevotella, Moraxella, etc. (Cabrera-Rubio et al).
Asthma	Proteobacteria, such as haemophilus, Moraxella and so on increased significantly.
Lung cancer	The largest groups of bacteria are Actinomyces and Peptostreptococcus.

Respiratory Viruses, Fungi and Respiratory Flora

Fungi, mainly *Aspergillus*, *Candida*, *Malassezia* and *Saccharomyces*, are distributed in the skin, intestine, mouth and lungs in the human body [46-48]. Studies have shown that the interaction between fungi and bacteria plays an important role in the establishment and restoration of microbial homeostasis [46].

Respiratory viruses are also involved in the occurrence and development of respiratory diseases, such as influenza virus, coronavirus, Boca virus, etc., can cause respiratory diseases. There is also a link between respiratory viruses and respiratory microbiota, and it has been reported that an increase in proteobacteria in the respiratory microbiota of influenza patients may aggravate the illness of the patients [49,50].

Respiratory bacteria, viruses and fungi are closely related, and the interaction between them should be paid attention to in the process of diagnosis, treatment and prevention of diseases.

Microbial Therapy of Respiratory Diseases

Probiotics are active microorganisms that are beneficial to the host and can improve the human microecological environment. So far, the probiotics that have been discovered can be divided into three categories: *Lactobacillus*, *bifidobacterium* and Gram-positive cocci. When the human body's probiotics

meet the needs, human health will be in a state of balance, if the probiotics lose balance, it may cause the human body to appear diarrhea, allergies, immunity and other symptoms, resulting in a series of diseases. Studies have shown that the pulmonary function of children with asthma can be improved by taking probiotic capsules containing *lactobacillus* and *bifidobacterium* [51]. Meanwhile, some experiments have also confirmed that respiratory flora can be changed by regulating the structure of intestinal microflora, which plays a positive role in the treatment of respiratory diseases [52,53]. Therefore, many chronic diseases can affect the course of disease by improving the intestinal flora, mainly through beneficial bacterial intake and microbial transplantation [54,55].

Probiotics ingested by the digestive tract can prevent a variety of respiratory diseases have been confirmed by many studies. Ten clinical trial studies covering multiple age groups have shown that probiotics can reduce upper respiratory tract infection rates [56]. A study involving children and adults in several parts of the world who were given probiotics and a placebo showed a reduction in the duration and number of days of illness, suggesting that probiotics could be an effective way to prevent disease. In addition to digestive tract intake, it can also be given directly to the respiratory tract [57] to change the microenvironment of the patient's respiratory tract and reduce the harm of pathogenic bacteria to the host.

Maintaining the homeostasis of respiratory tract flora and selecting suitable probiotics to regulate the respiratory tract mi-

environment are important contents in the prevention and treatment of respiratory diseases. Many respiratory diseases involve changes in microbial flora, so the study of respiratory flora will be a link that cannot be skipped.

There are many kinds of respiratory diseases, which are seriously harmful to human health, and it is an urgent disease to strengthen prevention and control. However, human's understanding of respiratory diseases is not deep enough, and the causes of diseases are still unclear. However, many studies have suggested that the role of microbial flora cannot be ignored. Therefore, further research on respiratory flora may provide a basis for revealing the occurrence and development of diseases.

With the upgrading of sequencing technology and the deepening and expansion of the field of bioinformatics, humans may have a more comprehensive understanding of the composition of respiratory microflora. There is a large number of microbial

communities in the respiratory tract to settle, in the disease control state, the composition and quantity of these microbial communities will also change, through microbial treatment can reduce and prevent the impact of respiratory diseases. However, there are still many problems that have not been effectively solved, such as the relationship between respiratory tract microbes and respiratory system diseases, the relationship between various microbial groups, the relationship between respiratory tract microbes and intestinal microbes, and the further development and application of probiotics. In short, the relationship between microbiota and respiratory diseases is still being studied, and this research will greatly promote the prevention and treatment of respiratory diseases. At the same time, there are still some shortcomings in this study. The respiratory diseases included in this study are not comprehensive enough, and there may be selection bias. Therefore, it is necessary to increase the exploration and supplement of related research to enrich the material.

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