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The Pathology, Epidemiology, and Current Therapy of Chronic Obstructive Pulmonary Disease (COPD)

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Abstract. Chronic obstructive pulmonary disease is a heterogeneous chronic respiratory disease with a high incidence worldwide. The pathogensis of COPD is complex, involving multiple factors such as airway infalmmation, abnormal or damaged alveolar structure, and abnormal immune cell function. The progression of the disease is also significantly influenced by factors such as microbial and immune imbalances. Moreover, the presence of COPD is considered a prognostic factor for various complications and metal health problems. As the world's third most deadly disease, COPD poses a great threat to people's health. Epidemiological research shows that the occurrence of COPD is affected by a variety of risk factors, especially external factors, such as smoking, air pollution, occupational exposure, etc. The incidence of the disease has been rising in many countries, bringing serious challenges to public health. At present, the main treatment strategies for COPD include drug treatment and non-drug intervention, such as bronchodilators, various prevention and control measures, etc., but there are still many limitations, such as different therapeutic effects and management difficulties. New targeted treatment strategies, the application of new technologies such as precision medical treatment and individualized treatment can better improve the quality of life of patients and promote the treatment level of COPD and other chronic diseases. Therefore, this article aims to review the pathological mechanism, epidemiological characteristics and existing treatment plans of COPD, and explore possible treatment directions in the future to provide a theoretical basis for clinical diagnosis and treatment.

Keywords: Chronic obstructive pulmonary disease, Pathology, Epidemiology, Treatment Stategies

1. Introduction

COPD constitues a foremost global cause of mortality [1,2]. Statistical data show that about 384 million patients worldwide have COPD [2], and the incidence and mortality of COPD are on the rise. In addition, the incidence of COPD is related to country, age and gender, and environmental risk factors of COPD are positively related to smoking and environmental pollution [3].

The pathological mechanism of COPD is complex, including chronic inflammatory reaction of the airway, alveolar destruction, protease-antiprotease imbalance, oxidative stress, etc [3,4]. Among

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them, tobacco smoke, air pollutants, occupational dust trigger chronic inflammatory reactions in the airways, promoting the aggregation of inflammatory cells and the release of various inflammatory mediators, resulting in airway remodeling and lung function decline [5]. The study found that the overexpression of inflammatory factors such as interleukin (ILs), IL-6, IL-8 and IL-17 is closely related to the incidence of COPD, forming a persistent vicious circle [5]. In addition, the reduction and abnormality of alveolar type 1 and type 2 cells cause the destruction of the alveoli structure, which leads to the occurrence of emphysema and affects the patient's respiratory function. At the same time, the progression of COPD also involves a variety of cell molecular mechanisms, such as Adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK) signaling pathway and hypoxia inducible factor-1 (HIF-1) pathway.

The existing treatment methods for COPD include drug treatment and non-drug interventions such as oxygen therapy and lung rehabilitation training. For example, bronchodilators, inhaled glucocorticoid (ICS), metformin can relieve patients' symptoms by dilating the airway and increasing air flow; non-drug prevention and control measures such as smoking cessation, respiratory rehabilitation, nutritional support can improve the patient's lung function and immunity. These methods can alleviate symptoms to a certain extent and temporarily enhance the quality of life of patients, but they cannot change the progression of the disease, and the long-term prognosis of patients is still not optimistic.

Therefore, a thorough understanding of the pathological mechanism of COPD and the exploration of new treatment strategies hold significant clinical implications [3,4]. To sum up, this article aims to summarize the pathophysiological mechanism, epidemiological trends, and existing treatment strategies of COPD, with the intention of providing a reference for the development of clinical treatment plans for COPD.

2. The pathophysiology of COPD

2.1. The characteristic and diagnosis of COPD

COPD is a prevalent chronic disease characterized by airflow obstruction and (or) emphysema, which can further progress to pulmonary heart disease and respiratory failure. The onset of COPD is usually related to environmental factors. Long-term exposure to polluted air and smoking can significantly increase the incidence of COPD. The main clinical symptoms of COPD include chronic cough, expectoration, breathing difficulties, and decreased exercise tolerance. These symptoms are usually caused by the long-term stimulation of the airways by harmful substances (such as smoking, air pollution, etc.), leading to airway inflammation and structural changes [1,5].

Chronic cough and sputum are usually the earliest symptoms of COPD patients. In the acute exacerbation period, the symptoms of COPD patients are aggravated dyspnea, increased frequency and severity of coughing and sputum, which may be accompanied by symptoms such as wheezing and chest tightness. This aggravation is usually caused by infections (such as bronchitis or pneumonia), air pollution or other environmental factors, which will also lead to a profound deteriotation of patient's quality of life [6]. In addition, patients who suffer from COPD may also be accompanied by other related symptoms, such as decreased physical strength and activity endurance, usually manifested as inability to carry out routine physical activities in daily life. Studies show that the decrease in active endurance of patients with COPD is positively related to their lung function. The worse the lung function, the lower the active endurance. This phenomenon of decreased endurance not only affects the patient's body and quality of life, but also may trigger psychological problems such as depression and anxiety [7].

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At present, the diagnosis of COPD is mainly composed of the following three indicators, the existence of risk factors, related symptoms, and persistent airflow obstruction shown by pulmonary function examination. Notably, lung function testing is indispensable in the diagnosis and staging of COPD. Specifically, by calculating the ratio of forceful exhalation volume (FEV1) and forceful vital capacity (FVC) in the first second, it can help determine whether there is airway obstruction. The decrease of FEV1 is usually a landmark feature of COPD, and the decrease in the ratio of FEV1 to FVC further confirms the irreversible obstruction of the airway [5]. The grading of FEV1 also provides a basis for the staging of COPD, which is crucial for clinical intervention and the selection of treatment plans.

In addition, high-resolution computed tomography (HRCT) is also important in the diagnosis of COPD. HRCT can clearly show typical characteristics such as emphysema, thickening of the airway wall and small airway lesions, which plays an important role in assessing the severity of the disease and formulating treatment plans. The most frequently identified imaging in COPD patients is emphysema , which is manifested as excessive dilatation of lung tissue and enlargement of the air cavity, resulting in decreased lung function [1]. The thickening of the airway wall reflects the chronic inflammation and remodeling of the airway, usually accompanied by lesions of the small airway. These changes can be detected at an early stage, prompting clinicians to intervene in time. Combined with imaging and pulmonary function testing data, different phenotypes of COPD can be better identified. With the in-depth study of the pathogenesis of COPD, more and more studies have begun to focus on the application of molecular markers in COPD phenotype identification, such as distinguishing between the phenotype of airway inflammation and the emphysema [2]. This combined method not only improves the accuracy of the diagnosis of COPD, but also provides the possibility for personalized treatment, making the treatment plan more accurate, and thus better improving the prognosis and quality of life of patients.

2.2. The molecular pathology of COPD

COPD is a disease characterized by limited airflow, and the destruction of alveolic structure is one of its important pathophysiological mechanisms. The destruction of the alveolar wall leads to emphysema, increased lung volume, and limited airflow, thus affecting the patient's respiratory function and quality of life. In COPD patients, the reduction of alveolar type I cells and the abnormal function of alveolar type II cells are important factors leading to alveolar damage. As the main cell of gas exchange, the reduction of alveolar type I cells will directly affect the intake of oxygen and the discharge of carbon dioxide, which will lead to dyspnea and hypoxemia. At the same time, the abnormal function of alveolar type II cells will affect the production of lung surfactants, further aggravating alveolar damage and airflow restriction.

Apoptosis, oxidative stress and endoplasmic reticulum stress are all involved in the process of lung alveolar damage. Apoptosis not only leads to the destruction of alveolar structure, but also triggers chronic inflammatory responses, further aggravating the degree of airflow limitation. Oxidative stress damages cell membranes and DNA by increasing the generation of free radicals, resulting in the decline of cell function. Endoplasmic reticulum stress is closely related to apoptosis, and it can activate multiple signaling pathways, ultimately promoting apoptosis and thereby exacerbating the damage and dysfunction of alveoli.In cellular levels, the airway inflammation of COPD is mainly characterized by the infiltration of neutrophils, macrophages and T cells. At the same time, the levels of inflammatory factors such as IL-1β and IL-17 in the airway of COPD patients increased significantly, and these cytokines are closely related to the persistence and aggravation of airway inflammation. Neutrophils and macrophages are not only the main effector

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cells of inflammatory reactions in the airway inflammation of COPD, but also further release the inflammatory reaction of the airway by secreting various inflammatory cytokines. This persistent inflammatory reaction will lead to damage to airway epithelial cells, which will lead to airway remodeling and dysfunction [8].

In addition, the activation of immune cells is also related to the pathological changes of COPD. T cells in the airway take part in the COPD process: they are involved in regulating and maintaining local immune responses, while abnormal immune responses may lead to tissue damage and disease progression. The activation of immune cells is also positively related to the severity of COPD. Mucoembolism in the airway reflects the severity and mortality of COPD, which suggests the importance of airway secretions in the pathological process of COPD [1].

Furthermore, in molecular level, the specific gene expression of cells in COPD patients undergoes significant changes, revealing the molecular pathways related to the disease progression. For instance, AMPK, as a sensor of the cell's energy state, can regulate the metabolic processes of the cell. HIF-1, under hypoxic conditions, regulates the adaptive responses of the cell and promotes the processes of inflammation and tissue remodeling. Mitochondrial dysfunction is also an important component of the pathological mechanism of COPD. Selective autophagy of mitochondria is pivotal in lung injury. This autophagy process helps to remove damaged mitochondria, prevent further damage to cell functions, and to a certain extent, alleviate the pathological changes of COPD [9].

The aggravation of oxidative stress is associated with the release of various cytokines. Pro-inflammatory cytokines such as IL-17A promote the proliferation and migration of airway smooth muscle cells, thereby exacerbating airway narrowing and the decline of lung function [10]. Additionally, the polarization state of macrophages also plays a crucial role in the pathology of COPD. The accumulation of M2-type macrophages indicates the complex relationship between inflammatory response and tissue repair.

Besides, oxidative stress and inflammatory reactions induced by smoking are considered to be important factors in promoting lung tissue degeneration. Oxidative stress not only leads to direct damage to cells, but also aggravates airway remodeling by inducing chronic inflammation, further aggravating the symptoms and progression of COPD.

2.3. The overview of COPD complications

COPD is closely correlated with the onset of kinds of diseases, and these complications not only affect the patient's quality of life, but also aggravate the course of COPD itself. Complications usually include lung cancer, pulmonary fibrosis, osteoporosis, systemic inflammation and psychiatric disorders. These complications further exacerbate the onset and progression of inflammation in the lungs by inducing various molecular and metabolic pathways. For example, lung lesions in COPD patients affect both bone metabolism and bone strength loss, especially in patients on long-term glucocorticoid use, who are more prone to osteoporosis, which puts them at a significantly increased risk of fracture [6].

Meanwhile, the presence of COPD is also regarded as an important prognostic factor. After cancer treatment, the mortality risk of COPD patients significantly increases, suggesting that in the management of cancer patients, the management of COPD comorbidities must be given due attention [7]. For instance, COPD may lead to higher postoperative complications and mortality rates for patients undergoing resection surgery or chemotherapy. Therefore, when formulating treatment plans, the respiratory function of the patients and the risks of cancer treatment need to be comprehensively considered.

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Additionally, COPD is also related to mental health problems such as depression and anxiety, and the presence of these mental illnesses may exacerbate the symptoms of COPD and lead to a worsening of the condition. Data from a study of middle-aged and elderly poeple aged 55 years and above living in Singapore showed that the 189 patients with COPD had higher rates of depression than those without COPD, and those who with depression had poorer health and lung function, and were more likely to have more severe respiratory problems [11].

Clearly,this shows that COPD patients experience depression at significantly higher rates compared to the general population, and the existence of depression will elevate the frequency of acute exacerbation of COPD, forming a vicious circle. Therefore, COPD patients should pay attention to mental health problems and psychological intervention, and receiving treatment necessarily.

3. The epidemiology of COPD

3.1. The analysis of COPD incidence

Approximately 384 million people in the world are affected by COPD, making it the third leading cause of death globally [2]. The cases and deaths rates of COPD vary widely across different regions and populations, mainly due to some factors such as smoking rates, environmental pollution, and occupational exposure. A study conducted in the rapidly developing areas of western China found that smoking was associated with a 1.6-fold increase in the incidence of COPD, and the incidence was higher in men. At the same time, with the accelerated development of industrialization and urbanization, air pollution has also become a primary public health crisis. Moreover, due to the lower development levels in rural areas compared to urban areas, some risk factors have also emerged, resulting in the prevalence of COPD in both rural and urban regions [12].

In addition, the COVID-19 epidemic has led to an increase in the hospitalization and mortality rate of COPD patients, especially in elderly patients, where COPD complications make them at higher risk after being infected with COVID-19 [3,13]. Therefore, although public health measures play an important role in slowing down the spread of COVID-19, the management and treatment of COPD patients still need special attention in order to reduce their morbidity and mortality during the epidemic.

In conclusion, as a global disease, the incidence and mortality of COPD are influenced by many factors, especially smoking and environmental pollution. With the acceleration of globalization, the prevalence trend of COPD urgently needs to be paid attention to. The formulation and implementation of relevant interventions should be combined with the characteristics of specific regions and populations in order to effectively reduce the incidence and mortality of COPD.

3.2. The risk factors of COPD

The occurrence of COPD is closely related to a range of risk factors, among which smoking is recognized as the main significant pathogenic factor. A large number of studies show that smoking is not only the main trigger of COPD, but also the severity of the disease in smoker is usually directly proportional to their smoking history. According to a study of patients with COPD, the lung function index of smokers is significantly lower than that of non-smokers, which shows that the damage to lung function caused by long-term smoking is irreversible. Smoking will also aggravate the inflammatory reaction of the airway, promote the progression of COPD, and further affect the quality of life and survival rate of patients [2]. In addition, air pollution, especially fine particles

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(PM2.5) and polycyclic aromatic hydrocarbons (PAHs), are also considered an important risk factor for COPD. Prolonged exposure to these pollutants will accelerate the decline of lung function, which will promote the occurrence and development of COPD by intensifying airway inflammation. For example, residents living in highly polluted areas have a significantly higher incidence of COPD than residents in low-pollution areas [14].

Furthermore, air pollution also increases the frequency of acute exacerbations in patients with COPD, leading to more hospitalizations and higher medical costs. Therefore, controlling air quality and reducing the emission of harmful substances is of great significance in preventing the occurrence of COPD.

Apart from smoking and air pollution, occupational exposure is also a significant risk factor for COPD. For instance, coal miners, construction workers, and workers in chemical plants face a higher risk of COPD due to long-term exposure to harmful dust and gases. A study on coal workers' pneumoconiosis combined with COPD showed that FEV1/FVC% of patients with COPD among coal miners decreased significantly, and their various lung function indicators were worse, with a higher incidence rate than the general population. This is closely related to the mineral dust and harmful gases they were exposed to during work [15].

Therefore, health monitoring and occupational safety measures for high-risk occupational groups are particularly important.

In addition, genetic susceptibility and age are also risk factors for COPD. Genome-wide association studies (GWAS) have identified many genetic mutations associated with COPD, such as cytokines IL-6, Tumor Necrosis Factor (TNF), antioxidant defense mechanisms (glutathione S-transferase) and so on [16]. And for those with a history of COPD in the family, the risk of developing the disease dramatically increases, suggesting that genetic factors play an important role in the pathogenesis of COPD. At the same time, the increase in age will also lead to a natural decline in lung function, further increasing the risk of COPD occurrence. Therefore, early screening and intervention measures for the elder population are also important strategies to reduce the burden of COPD.

4. Current therapeutic strategies targeting COPD

4.1. COPD treatment

Drug therapy serves as a pivotal factor in the management of COPD, mainly including bronchodilators, inhaled glucocorticoids and emerging drugs. Bronchiectants are the basis of COPD treatment. According to the Global Chronic Obstructive Pulmonary Disease Initiative (GOLD) guidelines, β2 agonists and anticholinergic drugs can dilate the airways, increase air flow, relieve airway spasms, alleviate shortness of breath symptoms, and improve the quality of life of patients [1],thereby effectively alleviating the breathing difficulties of COPD patients.

Secondly, inhaled glucocorticoids (ICS) have a significant therapeutic effect on some patients, especially COPD patients with airway inflammation. ICS can reduce the frequency of acute exacerbation, improve lung function, and promote the quality of life.

Notably, Metformin, as an oral hypoglycemic drug, not only lowers blood sugar levels, but also improve lung function through anti-inflammatory effects [7], which is effective in slowing down the progression of emphysema in patients with COPD. For COPD patients with diabetes, the application of metformin may improve their overall health. However, the drug treatment strategy for COPD needs to be individualized. Based on the severity of the patient's symptoms, the presence of

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comorbidities, the patient's response to the medication, and the treatment plan should be flexibly adjusted.

As a supplement to medication, COPD non-pharmacological therapy plays a considerable role in the treatment of COPD patients. Since smoking is a main cause of COPD, quitting smoking is considered as the most effective preventive and therapeutic measure. Doing this can not only slow down the progression of the disease, but also improve the overall health of patients. It can significantly reduce the acute exacerbation rate of COPD patients and improve their lung function [1]. After quitting smoking, respiratory rehabilitation for patients is carried out, including individualized exercise plans, nutritional guidance and psychological support, aiming to enhance the physical function and quality of life of patients, so as to improve exercise ability and reduce hospitalization rates.

Meanwhile, oxygen therapy can improve the state of hypoxia and enhance the quality of life of patients. Significantly, the prevention and treatment of osteoporosis should not be overlooked either. Due to the long-term use of glucocorticoids and chronic hypoxia, the incidence of osteoporosis in COPD patients is relatively high, increasing the risk of fractures. Systematic bone health management, including calcium and vitamin D supplementation, regular bone density checks, and appropriate exercise, can effectively reduce the incidence of osteoporosis [5].

4.2. COPD future therapeutic strategies development

Identifying the corresponding molecular markers is of vital importance for the development of targeted therapies and personalized treatment. For instance, inflammatory factors and nurtrophil extratrap-related molecules in the blood indicate the severity of COPD. Elevation of IL-6 and C-reactive protein (CRP) suggests acute exacerbation. The platelet count in the blood is also correlated with the decline in lung function and can be used to assess the changes in the condition and prognosis of COPD patients.

In respiratory secretions, the increase in the number of mucous embolism is consistent with the acute exacerbation and chronic inflammatory state of COPD, which may reflect the degree of airway inflammation and the disorder of secretion function, thus affecting the overall health status and treatment response of patients.

Furthermore, the development of RNA sequencing (RNA-seq) technology enables researchers to comprehensively and efficiently identify differentially expressed genes in lung tissue and blood, thus reflecting the pathological process of COPD. For example, by analyzing the transcriptome data of COPD patients, it is discovered that there are significant changes in the expression of specific genes, which are closely related to pathological mechanisms such as lung inflammation, oxidative stress and cell apoptosis. RNA-seq technology helps to identify COPD-related non-coding RNA and gene isomers, which can not only reveal the expression level of genes, but also provide information on the interactions between genes [16].

In addition, advancements in computational methods have enabled researchers to decompose cell-type-specific expression patterns from transcriptome data, providing a more refined basis for the classification of COPD [4,7].

5. Discussion

As a complex respiratory disease, COPD is mainly caused by factors such as smoking and environmental pollution, which has a wide-ranging impact on society and economy. Epidemiological research shows that the prevalence of COPD is increasing year by year, and it

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interacts with a variety of complications, resulting in a significant decline in the quality of life of patients. Therefore, the comprehensive management of COPD is particularly important.

The pathogenesis of COPD involves multiple cell types and molecular pathways, and its complexity makes it difficult to meet clinical needs with a single treatment strategy. Although current treatments are based on bronchodilators and smoking cessation, individualized and precise medical care still cannot be achieved.

However, the successive discovery of multiple potential targets (such as inflammatory mediators, oxidative stress pathways, epigenetic regulatory factors, etc.) has established a theoretical basis for COPD-targeted drugs discovery. Through a deeper understanding of the molecular mechanisms related to COPD, future treatments may become more personalized and can be tailored to the specific pathological processes of different patients.

It should be noted that there is obvious heterogeneity in the existing research. Differences in patient population, disease stage, or evaluation indicators among various clinical trials may make it difficult to directly compare the results. Moreover, epidemiological characteristics such as geographical and environmental factors may also affect the treatment response. Therefore, it is necessary to improve the comparability of the results through standardized design and combine omics technology and artificial intelligence analysis to ensure the reliability and wide applicability of the results.

In addition, environmental protection and public health measures also help to prevent the incidence of COPD and enhance the prognosis of patients. Strengthening the management of air quality, promoting healthy lifestyles, and providing effective smoking cessation support, among other measures, will provide an important guarantee for the prevention and management of COPD. At the same time, through policy guidance and public education, raising people's awareness of COPD can help reduce the exposure risk of high-risk groups, thereby reducing the burden of disease in an all-round way.

6. Conclusion

The prevention and treatment of COPD require a multi-dimensional and comprehensive approach. At the basic research level, this paper reviews and analyzes the molecular pathogenesis of COPD, including changes and destruction of alveolar structure, airway inflammation factors, providing a theoretical basis for the development of new targeted treatment and marking the treatment of COPD towards precision medicine and other directions. However, these innovative therapies still need to be verified by large-scale clinical trials before they can be turned into clinical practice.

Secondly, for the existing treatment strategies of COPD, such as drug treatment like bronchodilators and non-drug interventions for prevention and control, we should further improve and establish an individualized and accurate plan. At the same time, in terms of public health, it is necessary to understand the risk factors and implement measures such as strengthening tobacco control, improving air quality, and screening high-risk groups. In a word, the complexity of COPD requires us to constantly innovate and explore in research and treatment. Future research should focus on multi-dimensional intervention measures, integrating clinical practice with emerging technologies to provide more effective treatment plans for patients. At the same time, environmental protection policies and public health measures should be strengthened to fundamentally improve the prospect of COPD and bring better quality of life to patients.

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