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Abstract

Chronic obstructive pulmonary disease (COPD) is a common, preventable, and treatable chronic respiratory disease, which is characterized by persistent airflow limitation and respiratory symptoms. Pathological changes are mainly airway and/or alveolar structural abnormalities. Numerous factors, such as exposure to harmful particles or gases, genetic susceptibility, abnormal inflammatory responses, and abnormal lung development, are involved in the pathogenesis of COPD, those which determine the heterogeneity of COPD. Individuals show different pathophysiological changes, different disease evolution rules, and different clinical manifestations due to different etiologies, different susceptibility genes, and different chronic processes of “injury-inflammation-repair.” Therefore, disease managers need to conduct a multifaceted assessment of the whole body and the local area from the individual characteristics of COPD. With the sustained advancement of new technologies, from multiple perspectives, including genomics, exposomes, transcriptomics, mechanisms related to inflammation and immune regulation, microbiota, metabolomics, imaging features and radiomics, and the interaction of lungs and systemic organs to further explore the law of the occurrence and development of COPD, and finally, form an optimized prevention and treatment strategy. On the basis of thorough exploration, a COPD evaluation system that can meet clinical needs will be finally formed, so as to formulate scientific and effective individualized management strategies.

Keywords: chronic obstructive pulmonary disease, COPD pathogenesis, COPD diagnosis, COPD management

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a common, preventable, and treatable disease worldwide, characterized by persistent airflow limitation and
associated respiratory symptoms. Its pathological features are mainly chronic inflammatory changes in airway, lung parenchyma, and pulmonary vessels, which are usually associated with exposure to harmful particles and gases. Many factors, such as genetic susceptibility, abnormal inflammatory response, and abnormal lung development, are involved in the pathogenesis. In 2020, there were about 550 million (about 7.4%) COPD patients in the world, with the highest proportion of patients with COPD in Oceania (about 10.9%) and the lowest in Africa (about 5.4%) [1]. It mainly affects the population over 40 years old. Men and women are at equal risk. In 1990, COPD caused appropriate 2.4 million deaths. Until 2019, the global deaths rose to 3.23 million. About 80% of the deaths occurred in low- and middle-income countries, on the one hand, due to the high prevalence of smoking. On the other hand, it is difficult for the public and medical workers to obtain information on diagnosis and treatment management in terms of the low coverage of COPD diagnosis (69.8% in low- and middle-income countries, 98.1% in high-income countries) [2]. With the increasing smoking rate in developing countries and the aging population in high-income countries, the latest data of the World Health Organization show that the prevalence of COPD will continue to rise in the next 40 years with more than 5.4 million deaths from COPD and its related diseases annually by 2060. COPD has become an important public health problem in the world because of its high incidence, high mortality, and social and economic burden. Advances in pulmonary imaging have enabled more detailed understandings of airway and parenchymal abnormalities, and new endoscopic interventions are playing an increasingly important role in the management of advanced emphysema. At present, there is still no etiology-specific treatment for emphysema other than the addition of alpha 1 antitrypsin in patients with emphysema associated with alpha 1 antitrypsin deficiency. Further prospective studies could help clarify the role of inhaled corticosteroids in combination with dual bronchodilator therapy in the prevention of exacerbations. Compared with asthma, there is little hope for developing COPD-specific biotherapies. However, we still cannot give up investigation of COPD pathogenesis and developing scientific prevention and management methods. Therefore, this chapter focuses on the pathogenesis of COPD and the latest research advances in treatment and management of COPD.

2. Research advances in the pathogenesis of COPD

Clinical guidelines issued by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) tend to simplify the definition of COPD. COPD is actually a heterogeneous and complex disease. Smoking is globally recognized as the most important risk factor for COPD. But data from population-based studies show that only half of COPD cases are caused by smoking. Reports from South Africa, China, and South Korea indicate that the proportion of non-smoking COPD in men and women was different, and the morbidity of non-smoking COPD in women was more than 50%, suggesting that it may be related to household smoke exposure. COPD caused by exposure to biomass fuels is quite different from smoking-induced COPD in terms of phenotype, morbidity, and disease progression. Tuberculosis infection, occupational exposure, and frequent infections in children are also considered as major risks for the development of COPD. Agriculture is also a risk factor for COPD, where pesticide exposure is associated with accelerated decline in lung function, with a reduction of 6.9 ml per year in forced expiratory volume in 1 second (FEV1). In addition to environmental exposure, genetic risk factors are increasingly associated with the
development of nicotine addiction, chronic bronchitis, loss of lung function, and early lung development.

Unregulated inflammation, oxidative/antioxidant imbalance, proteolytic/anti-proteolytic imbalance, and imbalance of cell damage/repair are recognized mechanisms. At the same time, microbiota bias, air-pollutant-related damage, and autoimmune processes in lung tissue are all underlying pathogenesis of COPD. Epigenetic regulation has also been implicated in the pathogenesis of COPD.

2.1 Inflammatory mechanism

The pathological changes of COPD are characterized by chronic inflammation of airway, lung parenchyma, and pulmonary vessels. When the body inhales harmful particles and gases, it can cause a variety of inflammatory cells to participate in the release of a variety of inflammatory mediators, leading to irreversible lung damage. Damage to airway epithelial cells triggers a nonspecific inflammatory response through the release of endogenous intracellular molecules or risk-associated molecular patterns. These signals are recognized by pattern recognition receptors such as Toll-like receptors 4 and 2 on epithelial cells, resulting in the release of cytokines, such as TNF-α, IL-1β, granulocyte-macrophage colony-stimulating factor (GM-CSF), transforming growth factor (TGF) -β1, MCP-1, LTB 4, and IL-8. Inflammatory cells such as macrophages, neutrophils, eosinophils, and dendritic cells are recruited to sites of inflammation to form innate immune responses, while Th1, Th17, and ILC3 lymphocytes constitute acquired immunity. At the same time, activated inflammatory cells release a variety of inflammatory mediators. The mediators act on airway epithelial cells, which in turn promote epithelial cell damage. In patients with COPD, tissue damage by inflammation is uninterrupted, and the inflammatory response persists even after smoking cessation. In the case of chronic bronchitis, prolonged exposure to risk factors leads to mucosal and glandular inflammation, increased mucus secretion and epithelial cell proliferation, and altered tissue repair of the small airways.

Circulating blood cells, including neutrophils, and inflammatory cells in the lungs have long been implicated as players in smoking-induced tissue damage. Neutrophils in the sputum and bronchoalveolar lavage fluid (BALF) of patients with COPD are found to rapidly appear at sites of inflammation in response to interleukin (IL) -8, and neutrophil numbers increase with interleukin (IL) -6. A variety of other chemokines can induce neutrophil migration, including chemokines CXC motif ligand 2 (CXCL2), leukotriene B4 (LTB4), and formyl-met-leu-phe (fMLP), which are produced by the body’s own immune cells and diseased tissue cells and are related to host-microbe interactions. Alpha-1-antitrypsin (AAT) is the major anti-protease, which is also a candidate chemokine for neutrophils. Neutrophils are major destroyers of the elastic matrix of the alveoli. By secreting proteases and small cationic peptides, neutrophils are able to attack invading bacteria, viruses, pollutants, and in some autoimmune situations, their own tissues. Under the influence of environmental pollution (including cigarette smoke), enzymes and peptides released by neutrophils are able to cut collagen into pieces, thereby activating inflammatory cells and driving further chronic inflammation.

Circulating progenitors of pulmonary macrophages are originated from mononuclear cells in peripheral blood. When local inflammation occurs in the airways, monocytes migrate from the circulatory system to the lung tissue and differentiate into interstitial and alveolar macrophages. Pulmonary macrophages coexist with emphysematous areas and increase in number in the airways, lung parenchyma, BALF, and
sputum of patients. The number of macrophages in the airways is positively correlated with the severity of COPD. Macrophages can be activated by cigarette smoke extracts to release inflammatory mediators including tumor necrosis factor (TNF)-α, interleukin-8, other chemokines such as CXCL9, CXCL10, and CXCL11, monocyte chemotactic peptide (MCP)-1, LTB4, and reactive oxygen species. In addition, alveolar macrophages also secrete elastase including MMP-2, MMP-9, MMP-12, cathepsins K, L, and S, and neutrophil elastase extracted from neutrophils. Inflammatory proteins that are upregulated in macrophages during acute exacerbations of COPD are regulated by transcription factors such as nuclear factor-κB (NF-κB), activator protein-1, and tyrosine kinase c-Src.

T lymphocytes are present in the entire human organism including the epithelial surface of lung and mediate host defense. Human lungs are rich in resident T cells (more than 10 billion). Th1-type cells are involved in a sustained autoimmune response with interferon gamma as the primary cytokine and lead to exaggerated pro-inflammatory responses that result in uncontrolled tissue damage. Emphysema is generally considered to be a Th1 disease. Studies have shown that the development of emphysema may be mediated by T lymphocytes, and all T cell phenotypes are increased in smokers with COPD. Although neutrophils are the predominant cells in the lung parenchyma of non-COPD smokers, there is an increase in T cells (CD3 and CD8), primarily CD8 cytotoxic T cells, with evidence of emphysema. Apoptosis may be one of the mechanisms of pulmonary emphysema. In emphysema, CD8 T-cell numbers are correlated with the severity of tissue destruction, and their accumulation continues even after smoking cessation. In addition, the number of T cells was correlated with smoking history. In conclusion, the different interrelationships between T cell subtypes in COPD may be important for the progression of inflammation.

Airway eosinophilia and Th2-type inflammation are associated with allergic airway diseases such as asthma. However, recent studies have reported that 20–40% of COPD patients exhibit stable sputum eosinophilia. The SPIROMICS (SubPopulations and InteRmediate Outcome Measures In COPD Study) cohort has found that stable sputum eosinophilia is related to an increased frequency of disease exacerbations. In the meantime, high blood eosinophil levels at steady state predict a better therapeutic response to inhaled corticosteroids, which may be used to guide treatment. Although stable sputum and blood eosinophilia would be regarded as biomarkers of disease and steroid responsiveness, further work is needed to assess the importance of increased Th2 inflammation during COPD exacerbations.

2.2 Oxidative stress/antioxidant imbalance

ROS are oxygen-rich unstable molecules that can be either donors or acceptors of free electrons. Intracellular ROS can induce functional and structural changes in cells. The intracellular redox state is determined by the oxidant load in the respirable air and the pooling capacity of the lung protective mechanisms to absorb oxidants. Alveolar lining fluid, alveolar epithelial cells, local macrophages, and lung fibroblasts are all major targets of ROS. They can also be a secondary source of ROS. It showed that most cell types induce ROS production, and all lung cells may be involved in the redox state transition of COPD. The body keeps a dynamic balance between oxidation and antioxidation in normal condition. However, under pathological conditions, the imbalance between oxidation and antioxidation leads to oxidative stress, lipid peroxidation, protein modification, DNA damage, and activation of pro-inflammatory factors such as transcription factors NF-κB, which initiate inflammatory response.
and further promote oxidative stress. At the same time, the increase of oxidant can initiate the expression of antioxidant and anti-inflammatory genes through activation of nuclear factor E2-related factor (Nrf2). Therefore, antioxidant therapy may be effective in controlling and alleviating the symptoms and disease progression of COPD. Both outdoor environmental smoke and indoor air are sources of environmental ROS. For example, laser printers can significantly increase indoor air pollution from ozone and volatile organic compounds (VOCs), and appropriate filters may reduce this pollution. In addition, office buildings are carpeted with pesticides, and the use of caustic cleaning products can produce large amounts of inhalable chemicals and particles. Aerosol spray products, air fresheners, chlorine bleaches, cleaners, dry cleaning chemicals, and furniture and floor polishes may release VOCs and other toxic substances. Therefore, it is necessary to install proper ventilation and ventilation devices.

2.3 Imbalance of protease and anti-protease

Proteolytic enzymes have damaging and destructive effects on tissues, while anti-protease inhibits the activity of elastase. Imbalanced proteolysis is a plausible mechanism to explain the long-term persistence of emphysema. This theory partly explains the development of COPD. Proteolytic enzymes in healthy human lungs are resisted by anti-proteases. When exposed to cigarette smoke, this balance is broken and tends to proteolysis. Cigarette smoke or irritants derived from polluted air recruit inflammatory cells to produce protease 3, cathepsins L and S, MMP-2, MMP-9, and MMP-12, which are secreted primarily by neutrophils and macrophages. The anti-proteolytic barrier is composed of AAT, secretory leukocyte protease inhibitor, and tissue inhibitors of MMPs (TIMPs). Various modified forms of AAT (oxidized, aggregated, cleaved, nitrated, and citrullinated) have been implicated in inflammatory lung tissue destruction, of which proteolysis and ROS attack are major processes. Deficiency of α1-antiprotease causes an imbalance between protease and anti-protease, resulting in emphysema. In addition to proteolytic enzymes and inhibitory substances secreted by host inflammatory cells, bacterial enzymes and inhibitors should also be considered. In lung fibroblasts, elastase released by Pseudomonas aeruginosa activates the epidermal growth factor receptor (EGFR)/extracellular signal-regulated kinase (ERK) signaling pathway to promote IL-8 production by upregulating NF-κB. Besides proteases from neutrophils and macrophages, matrix metalloproteinases (MMPs) secreted by structural cells also play important roles in the pathogenesis of COPD. A number of MMPs members have been found to be involved in the process of COPD. Among them, MMP-1 is usually produced by fibroblasts, and MMP-8 is mainly expressed by neutrophils, both of which have collagenase activity and destroy the normal structure of alveolar septa. MMP-9 is produced by macrophages, neutrophils, and epithelial cells, not only to degrade ECM, but also to activate the immune response through the production of N-acetylproline-glycine-proline chemokines. MMPs can degrade almost all components of the extracellular matrix (ECM). ECM is hydrolyzed into peptide fragments that can promote local inflammation, which play a chemotactic role. For example, after MMP-12 degrades elastin, the peptide fragments have chemotactic effects on monocytes and fibroblasts, promote inflammatory responses, and accelerate lung tissue damage. Proteolytic products of ECM may perpetuate inflammation even after smoking cessation. Therefore, the level of elastin degradation products can be used as a good indicator of lung injury. As in COPD patients with α1 antitrypsin deficiency, a known genetic background (endotype)
with distinct clinical manifestations (phenotype) of emphysema leads to targeted therapeutic intervention (enhancing α1 antitrypsin). Major advances in lung imaging have paved the way to a new concept of COPD diversity. We need a more detailed understanding of the risk factors that contribute to these different endotypes and phenotypes to better describe therapeutic interventions.

2.4 Cell senescence and apoptosis

Cell senescence is an irreversible cell cycle arrest, which is a normal physiological phenomenon. Normal aging and emphysema share common pathophysiological features including the enlargement of alveolar space and the loss of elastic recoil. The accumulation of senescent cells in the body with aging leading to a senescence-associated secretion phenotype (senescence-related secretory phenotype, SASP) induces a pro-inflammatory state, which plays an important role in various age-related diseases. At present, the mechanisms of cell aging involved in COPD include oxidative stress, telomere shortening, mitochondrial dysfunction, activation of mTOR signal transduction, reduction of antiaging molecules, stem cell failure, and DNA damage repair defects. Cell senescence usually results in reduced proliferation with unchanged metabolic activity. This leads to increased inflammation and reduces cell regeneration, a process that is further accelerated by smoking and oxidative stress. Aging affects lung structures and inflammatory cells, fibroblasts, and progenitor cells, resulting in insufficient repair and regeneration. Defective clearance of apoptotic cells in patients with emphysema contributes to the persistence of pulmonary inflammation and increases the risk of acute exacerbation. It is also one of the important reasons leading to the progressive decline of lung function in patients. Autophagy dysregulation is present in cells from COPD patients as well. Insufficient autophagy results in the accumulation of the contents of damaged cells, causing senescence. In the normal lung, autophagy maintains a balance between organelle and protein production, degradation, and recycling. In COPD lung, chronic imbalance in autophagy leads to increased tissue senescence and insufficient repair.

2.5 Pathogenesis of COPD acute exacerbation

The common symptom of AECOPD is transient dyspnea, sputum suppuration, and increased sputum volume. Mild symptoms also occur, such as nasal obstruction, wheezing, sore throat, cough, fever, chest tightness, fatigue, insomnia, or physical activity limitation. In most cases, exacerbation in inflammatory airway is triggered by infection. Respiratory virus (rhinovirus, influenza virus, RSV, parainfluenza virus, human metapneumovirus, coronavirus, and adenovirus) infection is the main cause. Bacterial infection and environmental factors such as air pollution and ambient temperature also trigger or aggravate acute events. Meanwhile, heart failure, pneumothorax, pulmonary embolism, and anxiety cause acute exacerbation. Rhinoviruses account for 60% of exacerbations, which is the most prevalent predisposing factor. At present, it is believed that the antiviral immunity of COPD patients is impaired after respiratory viral infection, but the specific mechanism of aggravation of the disease is not fully understood. Bacteria are also extremely important in the pathogenesis of COPD exacerbations. Common species include the nontypeable Haemophilus influenzae, Moraxella catarrhalis, Streptococcus pneumoniae, and Pseudomonas aeruginosa, with Mycoplasma pneumoniae and Chlamydia pneumoniae occasionally present. The
application of microbiome technology has led to a new understanding of the interaction between the host and millions of microorganisms. 16S ribosomal RNA sequencing reveals that the lungs of healthy people and patients with COPD are colonized by rich, complex bacterial flora. The acute exacerbation is caused by the dysbiosis of preexisting bacteria in the lungs, rather than by the elimination of old species or emergence of new species [3].

AECOPD is also characterized by abnormal airway inflammation. Traditionally, airway eosinophilia and Th2-type inflammation have been associated with allergic airway diseases such as asthma. Recent studies have found that 20–40% of patients with COPD exhibit sputum eosinophilia. The SPIROMICS (SubPopulations and InteRmediate Outcome Measures In COPD Study) cohort has found that sputum eosinophilia in stable state is associated with an increased frequency of COPD exacerbations and deteriorations. In addition, the high level of eosinophil in blood indicates a better therapeutic response to inhaled corticosteroids, which may be used to guide treatment [4]. Although stable sputum and blood eosinophilia are considered as biomarkers of disease outcome and steroid responsiveness, further work is needed to assess the importance of increased Th2 inflammation during COPD exacerbations. In contrast to non-bacterial attacks, bacterial-associated COPD exacerbations result in airway neutrophilia and release of inflammatory mediators including IL-8, leukotriene B4, and TNF-α. Macrophages and T lymphocytes are also involved in the pathogenesis of COPD exacerbation.

These mechanisms mentioned above work together to produce two major pathologies: small airway pressure elevation and emphysema, which cause persistent irreversible airflow limitation. COPD is a chronic disease with high morbidity and mortality, which is a serious threat to human health. Because of its complex etiology and pathogenesis, at present, there are still no effective targeted drugs and treatments. We should further study the cellular and molecular mechanisms in the pathogenesis of COPD in order to detect the disease early and delay disease progression.

2.6 Epigenetic changes in the development of COPD

The imbalanced proteolysis theory is also supported by data from genome-wide association studies (GWAS) and gene expression studies. Recent COPD GWAS studies identified the following genome-wide locus that is strongly associated with the risk and development of COPD, including FAM13a at 4q22, the upstream enhancer of HHIP at 4q31, IREB2 and nicotinic acetylcholine receptors (CHRNA3 and CHRNA5) o at 15q25, the 19q13 locus with RAB4B, EGLN2, and CYP2A6, RIN3 at 14q32, MMP12 at 11q22, and TGFB2 at 1q41 [5–8]. Epigenetic changes includes, but are not limited to, posttranslational modifications of histones, DNA methylation, and RNA modification, which regulate gene expression without altering the gene sequence. Screening of miRNA and mRNA profiles in lung samples from smokers with or without COPD revealed that 70 miRNAs and 2667 mRNA differentially expressed. Several miRNAs, including members of the miR15/107 family, were found to regulate TGF-β signaling in COPD [9]. DNA methylation is an important regulator of gene expression, which is strongly regulated by environmental factors. DNA methylation analysis of small airway epithelia from COPD subjects found 1120 differentially methylated genes, mostly hypermethylated, which showed enrichment for three pathways: G-protein-coupled receptor signaling, arene receptor signaling, and cAMP-mediated signaling. The methylation status of 144 genes was negatively correlated with gene expression,
which involved in phosphatase and tensin homolog (PTEN) signaling, the nuclear factor erythroid-derived 2-related factor 2 (also known as Nrf2) oxidative stress response, and the effect of IL-17F on allergic inflammatory diseases [10]. The emerging role of epigenetics in the development of COPD will make it possible to reprogram, minimize risk, explain causes, and create new treatments for COPD.

3. Diagnosis of COPD

Patients with dyspnea, chronic cough and/or expectoration, a history of recurrent lower respiratory tract infections, and/or a history of exposure to risk factors are considered as COPD. Pulmonary function tests are necessary to confirm the diagnosis of COPD, such as forced expiratory volume in 1 second/forced vital capacity, FEV1/FVC < 0.70 after inhalation of bronchodilator, which can confirm the presence of persistent airflow limitation. Lung function assessed by forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), and the ratio of FEV1 to FVC (FEV1/FVC) reflect the physiological state of the lung, and these indices can be used to diagnose and monitor COPD. The goal of COPD assessment is to determine the degree of airflow limitation, the impact of the disease on the patient’s health, and the risk of long-term adverse outcomes (such as AECOPD, hospitalization, or death) to guide treatment. Spirometer is an important examination instrument for the diagnosis of COPD. Clinically, it is necessary to find indicators that can predict the occurrence and development of airflow limitation and comprehensively evaluate the respiratory physiology of COPD. Alveolar diffusion is the process of gas molecules exchange through the alveolar membrane (alveolar-capillary membrane). DLco was measured by single breath method to reflect the pulmonary diffusion function. Respiratory physiological indicators other than portable pulmonary function instruments can be supplemented to better assess COPD.

Recent studies have suggested that COPD may be caused by a decreased peak and/or an accelerated decline in lung function in early adulthood. COPD can start early in life and take a long time to manifest itself clinically, so identifying “early” COPD is difficult. In addition, the biological “early” associated with the initial mechanisms that ultimately lead to COPD should be distinguished from the clinical “early,” which reflects the initial perception of symptoms, functional limitations, and/or noted structural abnormalities. Pulmonary function tests are poorly correlated with clinical characteristics and lack sufficient sensitivity for early diagnosis. Meanwhile, due to the heterogeneity and phenotypic complexity of COPD, pulmonary function measurements provide limited information on prognosis, predictive outcome, and treatment strategy, which are not sufficient for accurate diagnosis, treatment, and efficacy evaluation. Patients with COPD often suffer from cardiovascular disease, skeletal muscle dysfunction, metabolic syndrome, osteoporosis, depression, anxiety, lung cancer, and other diseases. In view of the fact that these complications are independent risk factors for hospitalization and death, we should actively look for complications and give correct treatment to patients with COPD. The development of high-throughput technologies such as genomics, proteomics, and metabolomics has provided effective tools for elucidating global changes in complex inflammatory diseases such as COPD. Among them, COPD “omics” research mainly focuses on DNA (genetic) and RNA (transcriptome) markers. The advent of mass spectrometry (MS), including gas chromatography/MS and liquid chromatography/MS, has made proteomics and metabolomics more feasible for large-scale population studies. The
3.1 Metabonomics

Metabonomics is a comprehensive assessment of low-molecular-weight (< 1000 Da) endogenous metabolites, which can reflect biochemical reactions and metabolic changes under given physiological or pathophysiological conditions. Endogenous metabolites include a variety of small molecules such as sugars, lipids, steroids, and amino acids. The expression of these metabolites in humans represents the functional phenotype of cell, organ, or tissue. Metabonomics is of great help in identifying disease-related metabolites. Through the detection of various biological fluids (blood, urine, bronchoalveolar lavage fluid), it can provide help for the early detection of complex diseases and in-depth understanding of the pathogenesis of diseases. Smoking increases levels of nicotine and its metabolites, but also has a strong effect on the systemic metabolism of amino acids, lipids, and other small molecules. A study that recruited 211 subjects with COPD found that peripheral blood monocyte sphingolipid pathway enzyme expression and plasma small molecules such as ceramide were biomarkers of COPD and emphysema, even after adjustment for smoking. Subsequent targeted plasma metabolomics studies in 129 subjects with COPD genes further identified five sphingomyelins associated with emphysema and four trihexosylceramides and three dihexosylceramides associated with COPD exacerbations [11]. These findings support sphingolipids as potential new therapeutic targets for emphysema. Urine is also a common and available sample for metabolomics studies. Urine metabolomics is less invasive to participants than serum/plasma because serum metabolites remain relatively constant due to the balance of metabolism in the body, and urine samples are more suitable for metabolomics differential analysis than blood. Urine profiles of COPD patients and healthy controls were successfully isolated with ultrahigh performance liquid chromatography/MS (UPLC/MS)-based metabolomics. Ten metabolic biomarkers associated with COPD were identified in urine samples involving amino acid metabolism, lipid and fatty acid metabolism, and glucose metabolism. Amino acid metabolism is related to nutritional status, oxidative stress, and inflammatory response. Muscle dysfunction is an important feature of COPD patients, particularly during cachexia. In COPD patients, the concentration of histidine is increased, and muscle is synthesized by methyltransferase conversion to methylhistidine during cross-linking of actin and inosine [12]. Reduced use of histidine for muscle growth may result in increased serum histidine levels. In COPD patients, branched-chain amino acids (BCAAs) have been reduced; BCAAs regulate protein production and glucose homeostasis by continuously delivering BCAAs to skeletal muscle [13]. The reduction of BCAAs in COPD may indicate the risk of protein malnutrition. For underweight COPD patients, hypermetabolism caused by COPD exacerbation and respiratory muscle weakness is the main reason for the decline of BCAA concentration. However, the hydrolysis of muscle proteins and the consumption of branched-chain amino acids are part of the basic physiological function of providing carbon for gluconeogenesis during fasting. Cachexia patients with weight loss show increased gluconeogenesis [14], which will lead to increased consumption and decreased content of BCAAs in humans.
3.2 Proteomics

Proteomics aims to identify potential protein biomarkers of disease and has become a popular tool for both basic and clinical research. Proteomics has the potential to reveal some disease mechanisms that cannot be determined at the genomic level and has the great advantage of direct clinical relevance. Proteomic approaches have been used in many chronic lung diseases, such as cystic fibrosis, idiopathic pulmonary fibrosis (IPF), sarcoidosis, asthma, and so on. With the development of analysis and detection technology, the identification of potential protein biomarkers can be achieved in COPD research. Plasma proteins are involved in inflammation, coagulation regulation, lipid metabolism, and oxidative stress, and changes between healthy people and mild COPD can be evaluated at an early stage of the disease, helping us to identify early COPD. Currently, the most promising blood biomarker for COPD is sRAGE. sRAGE is an isoform of the advanced glycation end product (RAGE) transmembrane receptor that lacks a transmembrane domain through proteolytic cleavage. RAGE is encoded by the AGER gene, and SNPs in AGER have been associated with COPD and emphysema in targeted and genome-wide association studies [15]. RAGE binds damage-associated molecular pattern molecules to perpetuate inflammation in lung epithelial cells. In COPDGene, subjects with more severe emphysema had lower plasma sRAGE. The SNP in AGER (rs2070600) was associated with lower sRAGE plasma levels in COPDGene and other cohorts. Plasma sRAGE is a predictor of emphysema progressions, and it will be the first blood biomarker for emphysema to be submitted to the US Food and Drug Administration and the European Medicines Agency Biomarker Certification Program [16, 17]. While sRAGE is currently the best biomarker for emphysema, blood markers of inflammation are also associated with COPD severity and progression. In a study of 2123 subjects from COPDGene and 1117 subjects from SPIROMICS, plasma IL-6 and IL-8 were found to be positively associated with emphysema progression, but not with COPD severity and smoking status [18]. The detection of proteins in BALF and EBC can also help to clarify the pathogenesis of COPD and lung defense mechanism. In order to obtain an accurate diagnosis of COPD, an invasive approach is required in some cases. Lung tissue sample obtained by transbronchial lung biopsy or open lung biopsy procedure can also be used to analyze proteomic changes. Comparisons of lung tissues from COPD patients and healthy controls using MALDI-TOF-MS revealed significantly higher levels of matrix ferroproteinase-13 (MMP-13) and thioredoxin-like 2 in COPD patients, which may be more closely associated with the development of airflow limitation. In COPD patients, the level of SP-a in lung tissue was increased, and the level of SP-a in induced sputum supernatant was increased, but the levels of other surfactant proteins (SP-B, SPC, SP-D) were not changed. These results suggest that SP-a may be involved in the pathogenesis of COPD. However, the determination of a protein as a biomarker requires a large amount of sample data as a basis. We still have a lot of work to do.

3.3 Transcriptomics

The aim of transcriptome analysis is to capture coding and non-coding RNAs and quantify the heterogeneity of gene expression in cells, tissues, organs, and even the whole body. Transcriptomics can provide functional characterization and annotation of genes/genomes previously revealed by DNA sequencing [19]. Currently, three transcriptomics-related technologies are employed, including real-time quantitative PCR (qPCR), microarray, and RNA sequencing. The sample sources for the COPD...
transcriptomics study were focused on peripheral blood, lung tissue, and sputum. Similar to the epigenome, the transcriptome can be influenced by factors such as age, gender, cell type, environmental exposure, and disease status. For example, a study conducted microarray gene expression profiling of peripheral blood mononuclear cells collected from 136 COPDGene subjects and found that 1090 transcripts associated with FEV1% prediction and 1745 transcripts associated with FEV1/FVC, genes that overrepresent pathways associated with immunity, inflammatory response, and sphingolipid (ceramide) metabolism and signaling. At single cell level, COPD was found to be associated with a decreased ratio of specific transcriptome features of CD4+ resting memory cells and naive B cells [20]. There are also studies using gene expression profiling of lung tissue to explore the molecular pathogenesis of early COPD with emphysema. RNASeq was used to detect 16,676 genes expressed in lung tissue. Among them, 1226 genes in the COPD group with emphysema and 434 genes in the non-emphysema group were differentially expressed with healthy smokers [21]. Xiao et al. explored the relationship between gene transcriptomics and several single-nucleotide polymorphisms in sputum. Distal gene loci and biomarker encoding genes may influence circulating levels of COPD-associated pneumonia proteins, and a subset of these protein quantitative trait loci may influence their susceptibility in the lung and/or COPD. A notable feature of transcriptomics research is that the number of potential transcription variables is usually very large, and special methods are needed to deal with the huge and disordered data. For example, the weighted gene co-expression network and clustering method can be used to reduce the dimensionality.

COPD exacerbations are highly heterogeneous events associated with increased airway and systemic inflammation and physiologic changes, and reliable and objective biomarkers are invaluable to aid diagnosis and guide appropriate treatment. In blood, urine, breath samples (including exhaled breath, sputum, bronchoalveolar lavage fluid, and bronchial biopsies), levels of various immune inflammatory cells and molecules are elevated, such as CRP, PCT, BNP, plasma fibrinogen, IL-6, sputum eosinophilia, IL1β, CXCL10 (IP-10), some of which have been used in clinical examinations to assist in the evaluation of COPD deterioration [22]. At present, the research on the pathogenesis of AECOPD is still insufficient, and there are contradictory conclusions. In recent years, the widespread use of high-throughput sequencing technology has enabled us to study COPD in greater depth. At the metabolomics level, newly discovered markers of differential metabolism may be associated with disease states; at the proteomics level, several disease-related proteins have been identified and are expected to be used in the early diagnosis of COPD, while in transcriptomics, some biomarkers may be used to evaluate the prognosis of the disease. In general, multi-omics studies provide a way to discover biomarkers for early diagnosis of COPD, but the identified prospective biomarkers need to be clinically validated for early diagnosis of COPD. Therefore, clinicians need to collect a large number of patient data and clinical samples. Only by combining proteomics, transcriptomics, metabolomics, and bioinformatics, can we obtain reliable and helpful results for clinical diagnosis and treatment.

4. Research progress on prevention and management of COPD

4.1 Smoking cessation

Smoking cessation is the first step in the treatment of COPD and the key to reducing the progressive decline of lung function. Lung function and smoking-related
comorbidities (lung cancer and cardiovascular disease) increase mortality rate over time in COPD patients. Cooking with stoves instead of open fires can reduce the progressive decline in lung function by reducing indoor air pollution in a manner similar to smoking cessation. It is different for COPD patients with high tobacco dependence to smoking cessation. Thus, up to 40% of patients, even those with severe COPD, are persistent smokers. Drug therapy and nicotine replacement therapy can improve long-term abstinence rates. Smoking legislation and counseling by medical professionals can also improve abstinence rates. Currently, the effectiveness and safety of e-cigarettes as a smoking cessation aid are uncertain.

4.2 Physical activity

Increasing physical activity of daily living is as important as smoking cessation in reducing morbidity and mortality rate in COPD patients. In the early stage of the disease, lack of physical activity is closely related to hospitalization and mortality. In COPD patients, walking for 15 minutes per day reduced the risk of death by 14%, and an increase of 600 steps per day was associated with a lower risk of hospitalization. GOLD 2022 introduces the meta-analysis that included a total of 23 studies with 1663 participants. Compared with other groups, the mean deviation of 6 minutes walking distance (6MWD), FEV1 as a percentage of predicted values, SGRQ scores, and Chronic Respiratory Disease Questionnaire (CRQ) scores in Tai Chi group were significantly improved [23]. Tai Chi may have the potential to reduce dyspnea, improve exercise ability and quality of life in patients with COPD. Patients with COPD may benefit from practicing Tai Chi, but more effective programs need to be further studied.

4.3 Pulmonary rehabilitation

“Rehabilitation 2030” is a new strategic approach to prioritizing and strengthening rehabilitation services in the health system. As part of the WHO initiative, a series of rehabilitation interventions is being developed that includes pulmonary rehabilitation for COPD. Inpatient or outpatient pulmonary rehabilitation for patients with COPD is effective in improving multiple clinically relevant outcomes. There is evidence that the core components of pulmonary rehabilitation, including exercise training combined with disease-specific education and self-management interventions, can benefit almost every COPD patient.

Pulmonary rehabilitation is an effective multidisciplinary treatment strategy that improves dyspnea, exercise tolerance, and health-related quality of life. Classical exercise programs with individualized endurance and strength training remain the cornerstone of pulmonary rehabilitation, and education to promote behavior change and self-management are also necessary for successful intervention. Tele-rehabilitation has been proposed as an alternative to traditional methods. The results of multiple trials conducted in groups and individuals with multiple tele-rehabilitation delivery platforms (videoconferencing, telephone-only, websites with telephone support, mobile applications with feedback, centralized “hubs” for people to gather) show that tele-rehabilitation is safe and has similar benefits to center-based respiratory rehabilitation in a range of outcomes [24]. However, the evidence is still evolving and best practices have not yet been established.
4.4 Pharmacotherapy

Medical therapy for COPD is used to reduce symptoms, decrease the frequency and severity of exacerbations, and improve exercise tolerance and health. Maintenance drug therapy in the stable phase aims to improve symptoms, improve health-related quality of life, improve exercise intolerance, and reduce the risk of deterioration. In terms of airflow restriction, reduction of air entrapment, and improvement of exercise intolerance, inhaled long-acting beta2 agonists (LABAs) and long-acting muscarinic antagonists (LAMAs) have similar effects. LAMA tiotropium appears to be superior to LABA in preventing exacerbations and is as effective as the combination of inhaled corticosteroids and LABA. Therefore, LAMA monotherapy should be superior to LABA monotherapy in patients with a history of exacerbation. Acute exacerbations occurred significantly less during LABA-LAMA (indacaterol-glycopyrrolate) therapy than during LAMA (glycopyrrolate) monotherapy. Besides, the addition of LAMA and inhaled corticosteroids to LABA resulted in less aggravation than LABA and inhaled corticosteroids alone. Clinicians are concerned about whether further escalation from LABA-LAMA to triple therapy consisting of LABA, LAMA, and inhaled corticosteroids will provide additional benefits. Two large-scale studies found that triple therapy (LABA/LAMA/ICS) can reduce the death rate of COPD [25, 26]. For the benefit of fixed triple therapy for AECOPD, ETHOS research published evidence-based medicine evidence in the New England Journal of Medicine in June 2020. In this study, 8578 patients with chronic COPD were enrolled, aged 40 – 80 years, with smoking history of ≥10 packs/year, cat score ≥10 points, maintenance treatment with ≥2 inhalants before screening, maintenance treatment time ≥6 weeks, FEV1 estimated value ≥25% and <65%, and moderate or severe AECOPD history 12 months before screening; To compare the efficacy and safety of budesonide/glulomonium bromide/formforminhaled aerosol (MDI) and dual therapy (bud/form and gly/form) with two ICs doses, all cause death was the secondary endpoint; compared with laba/lama, the use of triple therapy containing high-dose ICs (not low-dose ICs) is associated with lower mortality. The results of this study have important clinical significance, and further research or analysis may help to determine whether specific patient subgroups show greater survival benefits. The potential benefit of reducing acute exacerbation by adding inhaled corticosteroids to LABA needs to be judged and weighed the potential risk of pneumonia. When fluticasone, an inhaled corticosteroid, is added to LABA, COPD patients with low eosinophil counts may have an increased risk of pneumonia. This suggests that there is a subgroup with a high eosinophil count, and the benefits of inhaled corticosteroids outweigh the risks. Clinicians must judge whether glucocorticoid treatment needs to be combined or stopped according to the clinical symptoms, acute exacerbation risk, asthma, bronchiectasis, pulmonary tuberculosis, blood eosinophils, and other indicators of patients, and select the route, dose, and course of glucocorticoid administration according to the heterogeneity of AECOPD. Eosinophils can predict the risk of acute exacerbation, and ICS has guiding value in preventing future AECOPD. The survey data showed that the blood eosinophil count was <100 cells/μl of COPD patients who were less likely to benefit from the treatment with the treatment plan containing ICS. In addition, the presence of Proteus, Haemophilus, and increased bacterial infections and pneumonia was associated with lower blood and sputum eosinophil counts. Therefore, a lower blood eosinophil count can identify characteristic individuals of the microbiome with an increased risk of clinical
deterioration caused by pathogenic bacteria. Higher blood eosinophils and lung eosinophils in COPD patients were associated with higher levels of type 2 airway inflammation markers. These differences in airway inflammation may explain the different responses of eosinophils to ICS therapy. The estimated value of eosinophil whose number is <100 cells/μl and ≥ 300 cells/μl can be used to predict the different probability of treatment benefit. It should be noted that the use of eosinophils, which can predict the efficacy of ICS, should always be combined with clinical assessment of the risk of acute exacerbation. In the population with low ICS use rate, a greater decrease in FEV1 was observed in mild to moderate COPD patients with high blood eosinophil count, which indicates that blood eosinophils can be used as a biomarker of decreased lung function and are not affected by ICS use. In young persons without COPD, higher eosinophil counts were associated with an increased risk of subsequent COPD [27]. In conclusion, blood eosinophils can help clinicians evaluate the possibility of beneficial preventive response to the addition of ICS to conventional bronchodilator therapy. Therefore, blood eosinophils count can be used as biomarkers combined with clinical evaluation when making decisions about the use of ICS. In view of the increasing importance of clinical features and individualized treatment decisions, further treatment options for this subgroup should be carefully examined.

Bronchodilator therapy (LABA, LAMA, or a combination of both) has been proved to be generally safe in randomized controlled trials. However, owing to these trials usually excluding patients who have severe heart disease, clinicians should be aware of the cardiac events reported in meta-analysis and observational studies. Patients reported that symptoms of chronic bronchitis may benefit from the addition of oral phosphodiesterase 4 inhibitor roflukast, especially those who have been hospitalized for COPD deterioration or have received more than two deterioration treatments in the outpatient department. Macrolide therapy is recommended for long-term and low-dose use in patients who have smoked. However, it is necessary to consider the side effects associated with propenolactone, the uncertainty of treatment for more than 1 year, and the resistance of bacteria to macrolides. The World Health Organization (WHO) has formulated the necessary intervention measures for COPD in low- and middle-income countries, and it pointed out that if the symptoms persist, low-dose theophylline can be added according to drug availability. Gold2022 suggests that FEV1 accounts for 35% ~ 60% of the estimated value, and COPD patients with smoking history are the best subjects for α1 antitrypsin deficiency (AATD) augmentation therapy (evidence level B). The existing clinical trials and registration data are almost completely concentrated on patients with ZZ (ZZAATD/PiZZ) genotype. Recent studies have shown that the risk of mild COPD in Z gene heterozygotes is increased. Different from ZZ genotype, Z gene heterozygotes will not develop COPD in the condition of non-smoking. Therefore, it is considered that quitting smoking can prevent the development of this kind of patients [28].

There are limitations in the evidence base of drug therapy for COPD. Almost all drug treatment studies included patients who had smoked for at least 10 years and excluded patients with asthma. It is not clear how effective COPD drugs are in patients who have never smoked or who have asthma. Due to the complexity of airway inflammation and related clinical phenotypes in COPD, a single inflammatory pathway or mechanism may not be enough to continuously inhibit inflammation in all patients with COPD. Each drug treatment plan should be individualized according to the severity of COPD symptoms, the risk of acute exacerbation, adverse reactions, complications, the availability and cost of drugs, as well as the patient’s response, preference, and ability to use various drug delivery devices.
4.5 Interventional treatments

For some patients with advanced emphysema whose medical treatment is ineffective, surgery or bronchoscopic intervention may benefit. Individualized treatment decisions should be based on the characteristics of emphysema, such as heterogeneous and homogeneous, complete lobar fissure or collateral ventilation. For most patients, the therapeutic effect needs to be combined with potential complications such as pneumothorax and pneumonia. Other interventions, including hot steam or sclerotherapy, can show some efficacy, but may lead to more complications. For patients with advanced COPD, lung transplantation is still an option to improve the quality of life and exercise endurance, but it has no effect on the overall survival rate. Palliative treatment is an effective method to control the late COPD symptoms.

4.6 Oxygen and ventilatory support

For patients with stable COPD and moderate decline of oxygenation index when they rest or exercise, long-term oxygen therapy should not be conducted routinely, but individual factors of patients must be considered when evaluating patients’ demand for supplemental oxygen. For patients with severe resting hypoxemia ($P_{aO2} \leq 55$ mmHg) or moderate hypoxemia ($P_{aO2} \leq 60$ mmHg) and signs of heart failure, pulmonary hypertension, or polycythemia, long-term oxygen therapy can improve their survival rate. The application of transnasal high flow oxygen therapy (HFNC) in the rehabilitation of COPD is a hot spot in recent years. A meta-analysis from 10 RCTs compared HFNC with conventional oxygen therapy (COT) or NIV in improving respiratory rate, $FEV_1$, tidal volume, oxygen partial pressure, total SGRQ score, 6MWD, and exercise tolerance time [29]. The comprehensive data of six studies showed that the respiratory rate of COPD patients in HFNC group was lower. The comprehensive data of three studies showed that $FEV_1$ of HFNC group was lower. There was no difference in tidal volume between patients with COPD in HFNC group and control group; There was no significant improvement in oxygen partial pressure between HFNC group and control group. In the subgroup analysis of HFNC and COT, the total score of SGRQ in HFNC group increased. Two multicenter RCTs showed an increase in 6MWD after HFNC, but no increase in exercise tolerance time. The differences in evidence quality included in this meta-analysis are prominent, which indicate that more high-quality RCTs are needed to verify these evidences. For patients with stable hypercapnia and high inspiratory pressure, noninvasive positive pressure ventilation aims to reduce the partial pressure of carbon dioxide ($P_{aCO2}$) in arterial blood by at least 20% or lower than 6.5 kPa, which can improve the survival rate. Therefore, patients who meet the condition and have a special home care environment can consider this method.

4.7 Treatment of comorbidities

Comorbidities affect a large part of patients with COPD. A cluster analysis was conducted on 213 COPD patients, and five unique clusters of comorbidities were established: (1) fewer comorbidities; (2) cardiovascular clusters, including hypertension and atherosclerosis, (3) cachexia clusters, including low body mass index (BMI), muscle atrophy, osteoporosis, and impairment of renal function; (4) metabolic clusters, including high BMI, dyslipidemia, hypertension, and atherosclerosis sclerosis; (5) psychological cluster, including anxiety and depression. Cardiovascular disease
is a common and important complication of COPD. Although the lung function is similar, there are important differences in dyspnea and quality of life in different clusters. Systemic inflammation in cardiovascular and metabolic clusters is at a high level. Lung cancer is common in COPD patients and is the leading cause of death. The United States Preventive Services Task Force (USPSTF) updated its recommendations for lung cancer screening in 2021, which recommend that conduct LDCT annual lung cancer screening for adults aged 50 ~ 80 who have 20 packs per year of smoking history and currently smoke or quit smoking within the past 15 years [30]. Osteoporosis and depression/anxiety are common complications of COPD, which are often missed, and are related to poor health status and prognosis. Gastroesophageal reflux is associated with increased risk of AECOPD and poor health. Overall, COPD combined with other that has a great impact on the prognosis. The existence of comorbidities should not change the treatment plan of COPD, and the comorbidities should be treated according to the conventional standard, which has nothing to do with the existence of COPD. When COPD is part of a multi-disease care plan, attention should be paid to ensuring the simplicity of treatment and minimizing multidrug treatment. Some drugs for COPD have been evaluated as well as the effects of treatment outside the lung. The inhaled combination of fluticasone furoate and vilanterol (an inhaled corticosteroid and a LABA) did not affect mortality or cardiovascular outcomes in patients with moderate COPD and increased risk of cardiovascular disease, but it improved cardiac insufficiency associated with hyperinflation. In a meta-analysis, there were fewer major cardiovascular events after roflukast treatment, but no randomized controlled study has been conducted to test the potential benefits of roflukast treatment on cardiovascular outcomes in COPD.

4.8 Treatment of exacerbations of COPD

Exacerbation of COPD is an acute exacerbation of respiratory symptoms (dyspnea, cough, expectoration, and suppuration) that requires a change in treatment strategy. AECOPD can be caused by a variety of factors, and the most common cause is viral or bacterial respiratory tract infection. Patients are often hospitalized with dyspnea as the main symptom. The exacerbation of respiratory symptoms in COPD patients needs to be identified as AECOPD or other causes. One important differential diagnosis is pulmonary embolism (PE). In a study that included 740 AECOPD patients, 44 patients were diagnosed with PE within 48 hours after being admitted to hospital [31]. Among the 670 patients who were considered to have no venous thromboembolism and did not receive anticoagulant therapy at the time of admission, five patients developed PE during the follow-up period, of which three patients developed PE related death. The overall case fatality rate in 3 months was 6.8%. In the patients with COPD admitted due to acute deterioration of respiratory symptoms, 5.9% detected PE using predefined diagnostic algorithms. Further studies are needed to understand the possible role of systematic screening for PE in this patient population. At the same time, cardiovascular events and pneumonia also need to be excluded during acute attack. The deterioration negatively affects lung function decline, health-related quality of life, and prognosis. The treatment goal of ECOPD is to minimize the adverse effects caused by this acute exacerbation and prevent the occurrence of acute exacerbation in the future. Recommended single-use short effect β receptor agonists with or without short acting anticholinergic drugs are the initial treatment for AECOPD. Short-term systemic glucocorticoid therapy (e.g., 40 mg prednisone for 5 days) with or without short course antibiotics is the preferred treatment for acute episode events. Severe exacerbations
require hospitalization and individualized treatment, including noninvasive ventilation support (preferred), oxygen therapy, treatment of associated diseases (such as heart failure, pneumonia), and finally, weaning or invasive ventilation. Cohort studies have shown that more than half of AECOPD patients have cardiovascular disease. Even without clinical symptoms of cardiac involvement, biochemical evidence of cardiac dysfunction (such as high concentration of troponin I or B-type natriuretic peptide) is common during treatment. About 20% of AECOPD may be due to the deterioration of underlying cardiovascular disease, and such patients have poor prognosis after admission. In Europe, 11% of patients died within 90 days after admission. The hospital stay of 50% of the patients was extended to 3 months; 35% of the patients were readmitted within 90 days. Gold2022 gives discharge criteria and follow-up recommendations: record the ability to perform physical activities during the follow-up of 1–4 weeks and consider whether the patient is suitable for participating in lung rehabilitation, at the same time, increasing protective measures such as wearing masks, reducing social contact, and washing hands frequently can reduce the frequency of AECOPD.

4.9 Vaccination

It is generally recommended that COPD patients receive influenza vaccine and pneumococcal vaccine. Influenza vaccine can reduce the incidence of lower respiratory tract infection; S. pneumoniae vaccine can reduce lower respiratory tract infection and prevent acute exacerbation of COPD. The Centers for Disease Control and prevention of the United States recommended supplementary vaccination for the patients with COPD who are not vaccinated with Tdap vaccine (dtap/dtpa) to prevent the occurrence of pertussis, tetanus, and diphtheria, in addition recommended that patients aged 50 and over with COPD should be vaccinated with herpes zoster vaccine. Novel coronavirus vaccine can effectively prevent SARS-CoV-2 infection. Patients with COPD should be vaccinated with novel coronavirus vaccine according to the national recommendations.

4.10 Brief summary

Due to the complex and heterogeneous COPD, there are individual differences in its clinical management. To this end, scientists have proposed a management strategy based on treatable characteristics (TTs), which can identify TTs according to their clinical characteristics (phenotype) and/or through effective biomarkers of specific pathological mechanisms (endotype) in the lung, extrapulmonary, and behavioral/environmental domains. TTs can coexist, interact, and change over time in the same patient (either spontaneously or as a result of treatment). Because TTs-guided management can improve clinical outcomes, the design of future trials for the treatment of early-onset patients needs to consider the presence or absence of TTs. Again, it is important to note that since endomorphs may differ with age, it may be different in early-onset and elderly patients, and the better understanding gained from the current study of early-onset COPD patients may provide guidance for future treatment guidelines.

5. Conclusion

Chronic obstructive pulmonary disease (COPD), as a common and heterogeneous respiratory disease, is characterized by persistent and incomplete reversible airflow...
limitation. Due to the heterogeneity and phenotypic complexity of COPD, traditional diagnostic methods can only provide limited predictive outcome and treatment information, which is insufficient for accurate diagnosis and evaluation. With the development of omics technology in recent years, genomics, proteomics, and metabolomics are widely used in the study of COPD, providing good tools for the discovery of biomarkers for diagnosis and elucidation of the complex mechanisms of COPD. In this chapter, based on the risk factors and causes of COPD, combined with metabolomics, proteomics, and transcriptomics studies reported in recent years, possible biomarkers for the diagnosis of COPD are summarized. It is expected to explore important metabolites and proteins involved in important pathways of COPD progression through protein-protein interaction and multi-omics analysis to explain the pathogenesis of COPD. Finally, the prospects and challenges of COPD diagnosis and treatment research are put forward. In the foreseeable future, on a global scale, COPD will remain a major public health problem. Population development in high-income countries and a significant increase in NCDs in low-income countries will accelerate this health burden, with risk factors largely unchanged. A better understanding of the genetic molecules and biology of the different endomorphs and phenotypes of this disease is needed to enable the development of innovative drugs.

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