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Review Article

Advances in metabolomics of chronic obstructive pulmonary disease

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is a chronic lung disease with limited airflow. COPD is characterized by chronic bronchitis and emphysema, and is often accompanied by malnutrition with fatigue, muscle weakness, and an increased risk of infection. Although the pulmonary function test is used as the gold criterion for diagnosing COPD, it is unable to identify early COPD or classify the subtypes, thereby impeding early intervention and the precise diagnosis of COPD. Recent evidence suggests that metabolic dysfunction, such as changes in lipids, amino acids, glucose, nucleotides, and microbial metabolites in the lungs and intestine, have a great potential for diagnosing COPD in the early stage. However, a comprehensive summary of these metabolites and their effects on COPD is still lacking. This review summarizes the metabolites that are changed in COPD and highlights some promising early diagnostic markers and therapeutic targets. We emphasize that intensified dietary management may be among the most feasible methods to improve metabolism in the body.

Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of mortality and morbidity worldwide.[1] COPD is a chronic lung disease characterized by expiratory airflow limitation that is not fully reversible along with chronic bronchitis and emphysema, and patients with COPD experience chronic cough, sputum, and sometimes wheezing. Inflammatory cell infiltration, mucus hypersecretion, and alveolar destruction are typical pathological features of the lungs in patients with COPD.[2] The quality of life in patients with COPD is greatly reduced because of the irreversible airflow limitation. The main risk factors for COPD include smoking and air pollution, and aging is also thought to be a risk factor.[3] COPD is one of the top three causes of death worldwide, and 90% of these deaths occur in low- and middle-income countries.[4,5] The heterogeneity of COPD and the limited availability of spirometry services result in the underdiagnosis of this disease.[6] Therefore, specific markers need to be identified for the early diagnosis, staging, and individual therapy. Metabolomics is a common approach in omics studies to analyze metabolites quantitatively and qualitatively in body fluids. Metabolomics uses modern techniques, such as nuclear magnetic resonance (NMR), gas chromatography–mass spectrometry (GC-MS), and liquid chromatography–mass spectrometry (LC-MS). This approach has high sensitivity, high resolution, and high throughput, and it provides instant access to human physiological and pathological conditions. Analyzing the metabolomics of COPD can help to identify multiple molecules that significantly change, thereby aiding in the diagnosis and treatment of this disease.

Over many years, researchers have focused on the molecules derived from humans in COPD metabolomics. However, recently, increasing evidence[7] has shown that metabolites from microbes, including pulmonary and intestinal microbes, could help us to understand the pathogenesis of COPD and the complex regulatory reactions toward this disease. Metabolomics research has enabled the early and easy identification of abnormal responses in the body during COPD, which aids in the categorization, early diagnosis, and primary prevention of this disease. This review summarizes advances in the metabolomics of COPD in the last 5 years, including lipids, amino acids, glucose, nucleotides, and microbial metabolites. Additionally, some promising diagnostic markers and therapeutic targets that may aid in the early diagnosis and intervention of COPD are discussed.

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Table 1
Changes in lipids, amino acid, glucose, and nucleotides in COPD.

Metabolism type	Changing substances	Sample matrix	References
Lipid metabolism	Sphingolipids increase	Plasma and sputum	8
	Ceramides increase	Plasma/serum, sputum, and lung of mice	9
	Glycosphingolipids increase	Plasma	8
	Cholesterol increases	Serum	12
	Free fatty acids decrease in early COPD	Plasma	12
	Fatty acid metabolites increase	Serum	12
	HDL decreases in severe COPD	Serum	15
	The ratio of two lipid metabolites (glycerophospholipid/sterol lipids decrease)	Serum	2
Amino acid metabolism	DID increases	Plasma, urine, and sputum	18,19
	Soluble EP increases	Lung of mice	20
	PGP peptide and its more potent acetylated form (acPGP) increase	Sputum, BALF, and plasma	21,22
	Heme increases	Plasma	23
Glucose metabolism	Airway glucose concentration increases	BALF and sputum	32
Nucleotide metabolism	AdNs decrease	Skeletal muscle	35
	Degradation products of AdNs (hypoxanthine, xanthine, and uric acid) increase	Sputum, serum, and urine	35–38
	Extracellular ATP increases	BALF	39,40
	cAMP decreases	Lung	41,42
	cGMP decreases	Lung	43
	Guanine metabolites (8-oxoGua, 8-oxodGuo, and 8-oxoGuo) increase	Urine	44

acPGP: Acetylated proline-glycine-proline; AdNs: Adenine nucleotides; ATP: Adenosine triphosphate; BALF: Bronchoalveolar lavage fluid; cAMP: Cyclic adenosine monophosphate; cGMP: Cyclic guanosine monophosphate; COPD: Chronic obstructive pulmonary disease; DID: Desmosine and isodesmosine; EP: Elastin peptide; HDL: High-density lipoprotein; 8-oxoGua: 8-Oxo-7,8-dihydroguanine; 8-oxoGuo: 8-oxo-7,8-dihydroguanosine; 8-oxodGuo: 8-Oxo-7,8-dihydro-2′-deoxyguanosine; PGP: Proline-glycine-proline.

Nutrient metabolism and COPD

Weight loss is often observed in patients with COPD and in smoking mouse models after 6 months. This finding suggests that patients with COPD may suffer from excessive nutrient depletion or inadequate energy, highlighting the essential role of food and energy intake for the maintenance of weight. The three major nutrients in the human body, namely protein, lipids, and glucose, not only are essential for activities and providing energy for anabolic and catabolic metabolism pathways, but also participate in immune regulation. Adenosine triphosphate (ATP), which is thought to be the center of energy conversion, plays an extremely important role in cellular energy metabolism. Nucleotide anabolism depends on specific glucose or amino acids. Many studies have found considerable variations in the concentrations of glucose and some amino acids and fatty acids in body fluids (including blood, urine, bronchoalveolar lavage fluid [BALF], and sputum). Certain nucleotides also change in the COPD population compared with individuals without COPD [Table 1]. These findings suggest that the three major nutrients and nucleotide metabolites are closely associated with COPD and act synergistically to play major roles in its development. The following section provides a detailed overview of the functions and regulatory mechanisms of various types of metabolites in the progression of COPD.

Lipid metabolism

Lipids are important biological molecules, and consist of phospholipids, cholesterols, and fats. Phospholipids are the main components of cell membranes, cholesterols are associated with hormone regulation, and fats can store energy. In addition, lipids serve as precursors for certain active metabolites. Recent studies have shown that concentrations of lipid metabolites in body fluids are altered in individuals with COPD.[8]

Decreased lung function is a major sign of COPD, and this is often accompanied by a decrease in total alveolar surfactant phospholipids and an increase in oxidative damage to lipid mediators.[2] The impairment of sphingolipid metabolism is common in COPD. Sphingolipids are representative of the phospholipid family and are exceptionally abundant within the tissue of superior animals. This impairment may be due to mitochondrial autophagy-mediated programmed cellular necrosis, which causes rupture of the cell membrane and injury of pulmonary tissue.[3] Ekroos *et al*[8] found elevated sphingolipid concentrations in the lungs of patients with COPD. Additionally, the number of metabolites of sphingolipids, namely long chain ceramides, was found to be surprisingly higher in individuals with COPD than in those without COPD. A lipidomic analysis of sputum samples also showed a higher level of 28 ceramides in smokers with COPD than in those without COPD.[9] Another study used a mass spectrometer to analyze exhaled breath, exhaled breath condensate, and induced sputum collected by non-invasive methods. These methods showed that sphingolipids, phosphatidylethanolamines, and sphingomyelins are higher in patients with COPD than in those without COPD.[10] Additionally, exhaled breath and exhaled breath condensate can differentiate smokers and non-smokers from patients with COPD.[10] However, the profile of exhaled breath condensate metabolism alone is insufficient to differentiate patients with COPD from healthy individuals.[11] In addition, the concentration of glycosphingolipids, which are another member of the sphingolipid family, is positively correlated with the exacerbation of COPD.[8,12] Interestingly, ceramide, which is a metabolite of sphingolipids, is positively correlated with the risk of cardiovascular disease.[13] Previous studies have also shown that sphingolipid metabolites can contribute to cardiac dysfunction. Therefore, studies need to investigate the coexistence of sphingolipid metabolites with cardiopulmonary disease, which is possibly due to a disorder of lipid metabolism.

Dysfunction of cholesterol accumulation, trafficking, and metabolism can also occur in patients with COPD, and some may develop hypercholesterolemia. Excessive cholesterol can exacerbate cigarette smoke-induced mitochondrial damage and contributes to cellular energy deficiency. In contrast, mitochondrial function in patients with severe COPD is negatively correlated with serum concentrations of triglycerides and metabolites of fatty acids.[14] The metabolites of fatty acids include myristic acid, phytic acid, palmitoleic acid, and heptadecanoic acid. Concentrations of high-density lipoprotein (HDL), which is not only involved in lipid metabolism, but is also integral to the

body's immune and antioxidant defense, are decreased in the plasma of patients with COPD.[15] There are also differences in polyunsaturated fatty acid metabolism between individuals with COPD and individuals without COPD. These findings suggest a higher level of oxidative stress and an inflammatory state in COPD. Fatty acids are activated in large quantities for more energy through the beta-oxidative pathway when the glucose supply is dysfunctional. At this time, the body is already heavily affected by the disease. However, different studies have shown different results regarding whether the total fatty acid concentration is increased in the circulation of patients with COPD. This phenomenon may be explained by the assumption that subjects in different studies had different stages of COPD.

Concerning fat in COPD, some studies have shown that fat initiates the synthesis of pro-inflammatory molecules and impairs lung function, as well as increases the severity of COPD.[16] Other studies have shown that fat has a protective effect on chronic lung disease. This protective effect is based on evidence that overweight individuals show a better prognosis than those with a lower or even normal weight, which is the so-called "obesity paradox".[12] Considering that obesity and increased fat levels are generally associated with negative outcomes and increased severity of lung diseases, we believe that the former view appears to better reflect the actual situation observed in COPD clinically. The role of specific fatty acids in the progression of pulmonary and cardiovascular metabolism disorders or COPD is unclear. Increased dietary fatty acid intake generally worsens expiratory flow in patients with COPD, while certain fatty acids, such as dietary pentadecanoic acid, help improve lung function. Lauric acid is increased in the circulation of patients with severe COPD, and it beneficially regulates cholesterol, insulin resistance, and inflammation.[2] In addition to changes in single lipid metabolites, the ratio of two lipid metabolites has been an area of research interest. Researchers have found that the area under the curve of certain plasma glycerophospholipid/sterol lipid ratio reaches nearly 1 for COPD.[2] Additionally, the monocyte and HDL ratio is elevated in COPD. Both of these ratios are promising potential markers for the diagnosis of COPD.[17]

COPD lipid metabolism disorders result in lipotoxicity via increasing accumulation of metabolites. This metabolite accumulation locally disrupts the structure of pulmonary parenchyma and impairs lung function. Additionally, this accumulation systemically causes cellular energy deficiency and fatigue by mediating mitochondrial damage. Studies have shown that cardiac and pulmonary diseases share similar disorders of lipid metabolites. The findings mentioned above indicate that beneficial lipid metabolites, such as polyunsaturated fatty acids, or recovering abnormal lipid metabolism pathways may be beneficial for simultaneous alleviation of cardiopulmonary comorbidity.

Amino acid metabolism

In addition to lipids, proteins are also important nutritional and immunomodulatory sources. Proteins participate in the synthesis of many biologically active substances within the body, supplying organs with energy, and regulating immune responses. Amino acids are metabolites of protein catabolism and are also involved in many types of metabolic regulation.

Some protein metabolites are abnormally increased in COPD. Desmosine and isodesmosine help maintain the structure of the lung matrix and are specific to the mature elastin of alveoli. Desmosine and isodesmosine are released into the blood as metabolites owing to the destruction and degradation of the alveolar parenchyma in patients with the emphysematous phenotype.[18,19] In addition, soluble elastin peptide is produced during the occurrence of massive protein hydrolysis in the lungs. Elastin peptide can drive and maintain the diffusion of the inflammatory process during COPD.[20] Several researchers observed varying high concentrations of desmosine and isodesmosine and elastin peptide in the circulation of patients with COPD, which is in accordance with the viewpoint mentioned above. The neutrophilic chemokine proline-glycine-proline (PGP) peptide and its more robust acetylated form, acPGP, are increased in bronchiolar lavage fluid from patients with COPD.[21] PGP is initially cleaved from collagen by matrix metalloproteinases 8 and 9. PGP and acPGP with chemotactic activity cause inflammatory cells to accumulate in the lungs and consequently cause the destruction of the pulmonary parenchyma. The concentration of acPGP in sputum is positively correlated with airflow limitation, the severity of emphysema, and the risk of acute exacerbation of COPD at 1 year of follow-up.[22] There are many toxic and oxidative ingredients in cigarettes. Therefore, erythrocytes from the circulation in patients with COPD and a long smoking history are easily destroyed owing to oxidative damage. Studies have shown that the heme in plasma from patients with COPD (Global Initiative for Chronic Obstructive Lung Disease Stage 4, GOLD 4) is increased. Free heme also causes lipid peroxidation and endoplasmic reticulum stress by producing redox-active iron and reactive molecules. Long-term endoplasmic reticulum stress accelerates the onset of pulmonary fibrosis and emphysema. Treating mice with COPD using heme-clearing protein reduces endoplasmic reticulum stress, pulmonary fibrosis, and emphysema owing to the removal of heme in plasma.[23]

Essential amino acids are inadequate in COPD.[24] Certain amino acids can beneficially accelerate the repair of damage in COPD. Therefore, an exogenous amino acid supplement should be taken into consideration to alleviate COPD symptoms. The extra-pulmonary symptoms of COPD are often associated with reduced muscle mass, loss of muscle strength, and mitochondrial dysfunction. This situation leads to earlier and greater dependence on glucose metabolism for muscular cells, which in turn causes muscle acidosis and fatigue earlier during exercise. Carnosine has the potential to delay the onset of muscle acidosis and decrease antioxidant/carbonyl stress in patients with COPD. Carnosine is synthesized by β-alanine and L-histidine, which are catalyzed by carnosine synthase in the body. Carnosine is decreased in patients with severe to extremely severe COPD. A random, double-blind, placebo-controlled trial showed that a β-alanine supplement increased muscle carnosine in patients with COPD without side effects.[25] Another study showed that a supplement with 4.0–4.5 g histidine daily from the diet was associated with decreased pro-inflammatory cytokines, little oxidative stress, and glucose homeostasis. Moreover, supplemental histidine can improve cognitive function by metabolizing histidine to histamine.[26] Leucine has insulinotropic properties and enhances the anabolic capacity of dietary proteins.[27] A clinical trial investigated leucine and lipid supplements for patients with COPD and a low muscle mass. This trial showed that supplying nutrient intervention improved nutrients in plasma, exercise capacity, and the overall health status. However, leucine failed to improve long-term exercise capacity in patients with moderate COPD who suffered from muscle wasting.[28] Therefore, whether amino acid supplementation is helpful for patients with COPD requires further investigation.

A disorder of amino acid metabolism in COPD often induces excessive harmful peptides or amino acid metabolites because of lung parenchymal destruction and an inflammatory response. These disordered metabolites in turn aggravate the pathological destruction of the lungs. Patients with COPD also show a reduced capacity for the synthesis of the antioxidant carnosine in myocytes. In the case of impaired exercise capacity, and inadequate dietary supplementation of essential amino acids, muscle mass and strength are impaired. The antioxidant N-acetylcysteine inhibits the effect of reactive oxygen species, reduces lung oxidative damage, slows cellular senescence, and prevents the development of emphysema.[29] N-acetylcysteine might be applied to regulate amino acid metabolism clinically in COPD in the future.

Glucose metabolism

Glucose supplies the body with energy during exercise and is the main source of energy for the brain and nerves. In addition, most of the body's energy is from the oxidative metabolism of glucose. Glucose catabolism breaks down glucose into smaller molecules. This metabolic

process can quickly produce a sufficient amount of energy for cells. Glycogen is a storage form of glucose and is primarily synthesized in skeletal muscle and liver cells. Patients with COPD are prone to feel chronic fatigue. They experience muscle weakness and inadequate cellular energy supplements, which suggest a disturbance in glucose metabolism.[30]

Glucose metabolism plays a crucial role in triggering immune response. When pathogens invade the lungs, neutrophils rapidly accumulate in the irritated tissue during intrinsic immunity as the second line of the body's defense. Using radioactive flux analysis and liquid chromatography-mass spectrometry (LC-MS) tracing of U-13C glucose, glutamine, and pyruvate, researchers found that neutrophils relied on glycolysis for rapid ATP production. Neutrophils are then capable of carrying out efficient phagocytosis and kill the invaded pathogens. This process requires sufficient intracellular glycogen storage derived from the gluconeogenesis pathway. However, glycogen in neutrophils is reduced and is dysfunctional during COPD.[31] Therefore, an insufficient glycolytic energy supplement fails to effectively stimulate the immune response against COPD, resulting in continuous bacterial colonization and inflammation. Airway glucose concentrations are normally 3–12 times lower than circulating glucose concentrations. High glucose concentrations are detected in the sputum of patients with COPD.[32] Studies have shown that more glucose in the airway impairs host immunity by reducing epithelial resistance towards bacterial invasion. Fewer immune proteins and increased glycosylation of epithelial cells are observed in COPD. Additionally, high glucose concentrations provide a suitable environment for bacterial growth,[32] which suggests that glucose concentrations in the airway are related to the pathogenesis of COPD.

COPD often coexists with metabolic syndrome. COPD is prone to increased concentrations of pro-inflammatory mediators and adipose tissue hormones, such as leptin. Therefore, insulin resistance and chronic hyperglycemia easily occur. Chronic hyperglycemia, in turn, leads to more glycosylation products, which accelerates the synthesis and deposition of pulmonary collagen and causes COPD. Some studies have shown that glucagon-like peptide 1 (GLP-1), which is produced by intestinal cells, stimulates the secretion of insulin from pancreatic β-cells. GLP-1 helps resist insulin resistance, positively regulates glucose metabolism, and normalizes fat metabolism.[33] Developing methods to prolong GLP-1 activity or supplying exogenous GLP-1 may improve glucose and lipid metabolism in COPD.

Glycolysis and lipolysis can produce energy for cells. However, glycolysis is better and faster at producing ATP than lipolysis. When immune cells produce energy in a glycolytic manner, they might produce a large amount of the antioxidant nicotinamide adenine dinucleotide phosphate (NADPH) via the pentose phosphate pathway. This pathway represents quicker cell differentiation and greater capacity for pathogen clearance than the fatty acid oxidation pathway.[34] On the basis of this weakened capacity to clear pathogens for immune cells in patients with COPD, we speculate that the energy production mode of cells in COPD tends to be fatty acid oxidation or there is a conversion from glycolysis to fatty acid oxidation. Therefore, further investigation of key molecules regulating this conversion may be a new target for the intervention of COPD in the future.

Nucleotide metabolism

Nucleotides act to synthesize hereditary substances. Many single nucleotides have a variety of important biological functions and are closely associated with substance and energy metabolism. Nucleotide metabolism consists of purine metabolism and pyrimidine metabolism, and recently, researchers have paid more attention to purine metabolism in COPD.

Decreased concentrations of adenine nucleotides (AdNs), especially ATP concentrations, are a common feature of skeletal muscle atrophy in COPD. Researchers have shown decreased AdN concentrations and the accumulation of their metabolites (hypoxanthine, xanthine, and uric acid) in disused and atrophied skeletal muscle.[35] This finding confirms the presence of dysregulated AdN metabolism in COPD. Elevated concentrations of other adenosine metabolites are also found in COPD. Hypoxanthine and xanthine are substrates of xanthine oxidase, and xanthine acts to promote oxidative stress. One study analyzed sputum supernatant from 980 healthy non-smokers, smokers with preserved lung function, and patients with COPD, and showed a strong correlation between hypoxanthine concentrations and the severity of COPD.[36] However, the relationship between mildly elevated serum uric acid concentrations and the incidence of COPD remains unclear.[37,38] ATP plays an important role in cellular metabolism and inflammatory processes. Before extracellular ATP is degraded, it acts on target cells by activating P2 purinergic receptors on the cell surface. In obstructive airway diseases, such as COPD, excessive extracellular ATP activates pulmonary vagal nerve endings and induces bronchoconstriction.[39] Therefore, blocking P2 purinergic receptors can significantly inhibit the activation of ATP in isolated nodose pulmonary vagal afferents in the lungs.[40]

Cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) are intracellular second messengers. They are involved in the regulation of substance metabolism and the biological functions of cells. The quantity and function of cAMP and cGMP are abnormal in COPD. cAMP inhibits transforming growth factor-β1 mediated epithelial-mesenchymal transition, which occurs in the lung epithelium in some patients with COPD. A 4-week phase IIb clinical study showed that the inhibition of cAMP hydrolysis by phosphodiesterase inhibitors (e.g., ensifentrine) alleviated patients' bronchial symptoms.[41,42] cGMP is decreased in the lungs of patients with COPD. Activating the nitric oxide-cGMP pathway is beneficial for alleviating emphysema. Nitric oxide activates soluble guanylate cyclase to produce more cGMP, which further activates cGMP-dependent protein kinases that regulate apoptosis and migration. Riociguat alleviates the phenotype of emphysematous mice because it promotes the nitric oxide-cGMP pathway.[43] In a study of urine in patients with COPD, three guanine metabolites were measured using LC-MS/MS. These metabolites were 8-hydroxyguanine, 8-hydroxy-7,8-dihydro-2′-deoxyguanosine, and 8-hydroxy-7,8-dihydroguanosine. This study showed that concentrations of all three metabolites were significantly elevated, among which 8-hydroxy-7,8-dihydroguanosine was the most extraordinarily sensitive biomarker of oxidative stress in urine according to an area under the curve analysis.[44]

At present, research on nucleotide metabolism related to COPD is mostly limited to nucleotide itself, except for ATP, which has been reported to be involved in almost all types of metabolic processes. Few studies have reported the association of nucleotide metabolism with other types of metabolism. Whether nucleotide metabolism affects the process of lipid metabolism, amino acid metabolism, and glucose metabolism is unknown. Additionally, whether nucleotide metabolism affects the intermediate products of different metabolic interactions and whether it affects conversion among different metabolic types by affecting the gene expression of metabolism-related enzymes are still unknown. Further studies are required to identify the code of complex communication among various types of metabolism.

Microbial metabolism and COPD

Beyond the common metabolic disorders mentioned above, attention has been paid to the role of microbes and their metabolites in the pathogenesis of COPD in recent years. In patients with COPD, their lower airways are susceptible to bacterial colonization owing to the impaired function of mucus elimination out of the airways. In addition to pulmonary microbes, intestinal microbes and their metabolites can also invade the lungs and show a difference in the blood circulation [Fig. 1].

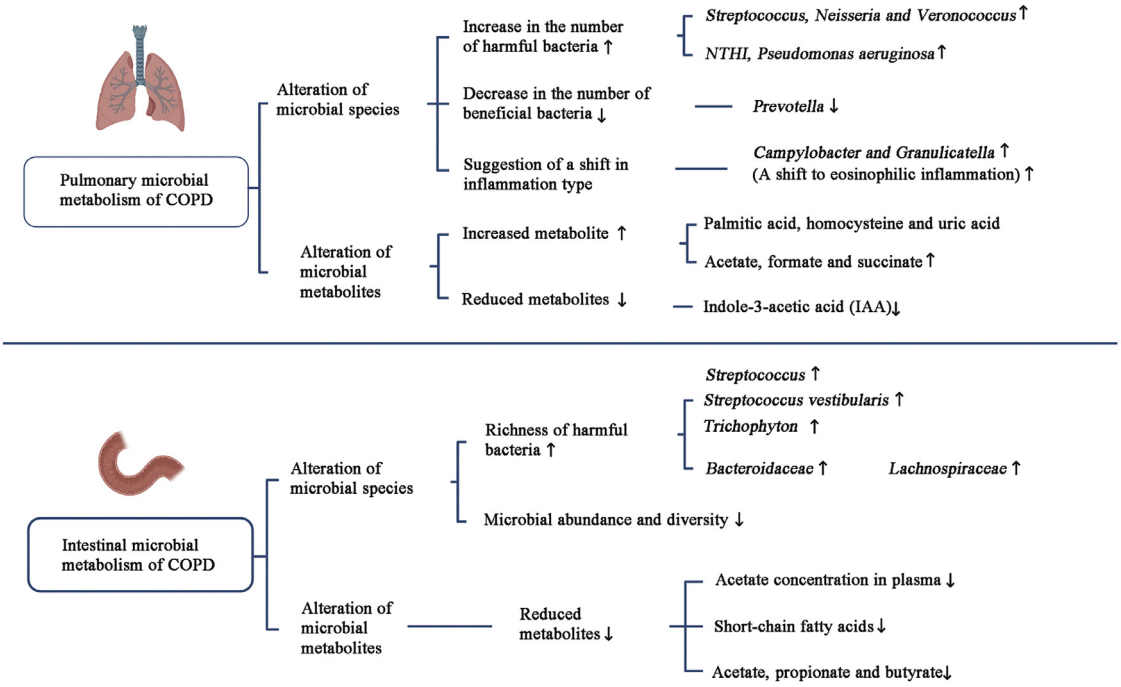

Fig. 1. Changes in pulmonary and intestinal microbes and their metabolites in COPD. COPD: Chronic obstructive pulmonary disease; NTHi: Non-typeable *Haemophilus influenzae* (*H. influenzae*).

Pulmonary microbial metabolism

Healthy human lungs were originally considered to be sterile. However, in recent years, increasing evidence has shown that diverse resident microbes are present in healthy lungs. The abundance and diversity of pulmonary microbes are altered in chronic lung diseases compared with healthy individuals, but the role of pulmonary microbes and their secretions in COPD remains largely unknown, for some reasons like poor access to pure samples and limited amounts of microbes detected.

The diversity and abundance of microbes in the lungs of patients with COPD differ from those of healthy individuals. The occurrence rate of reduced lung function is positively correlated with the quantity of *Streptococcus, Neisseria,* and *Veronococcus.* In contrast, *Prevotella* is positively associated with better lung function, non-COPD, and fewer symptoms.[45] A cohort study that consisted of 181 participants with COPD and a mean 4.5-year follow-up showed that the most common bacteria in the respiratory tract was non-typeable *Haemophilus influenzae* (*H. influenzae*), followed by *Pseudomonas aeruginosa.* Additionally, after correction, *Streptococcus pneumoniae* colonization was positively correlated with *H. influenzae* colonization.[46] In some patients, neutrophilic and eosinophilic-typed COPD are interchangeable. A time series analysis of the microbiome showed that *Campylobacter* and *Granulicatella* were positively correlated with eosinophilic-typed COPD instead of the common neutrophilic-typed COPD. Therefore, the quantity of *Campylobacter* and *Granulicatella* increases with time. An increased quantity of these two microbes suggests that a shift from neutrophilic to eosinophilic inflammation is occurring in patients with COPD, which is consistent with higher sputum eosinophilia observed clinically.[47]

In addition to direct effects, pulmonary microbes affect the development of COPD by secreting metabolites indirectly. An important hypothesis related to this indirect effect is that altered tryptophan metabolism of *Lactobacillus* in the airways is associated with a reduction in indole-3-acetic acid (IAA). *In vitro* and *in vivo* studies have shown that airway microbiota-derived IAA attenuates neutrophil inflammation and emphysema. IAA also improves lung function via an interleukin-22-mediated macrophage–epithelial cell interaction pathway.[48] In contrast, weakened tryptophan catabolism of *Lactobacillus* in the hypoxic environment of COPD results in decreased IAA production. This decreased IAA production further induces inflammation, epithelial cell apoptosis, and impaired lung function.[48] Functional studies of the airway microbiome in patients with COPD have suggested that Proteobacteria, Actinobacteria, and Firmicutes are major contributors to the biosynthesis of palmitic acid, homocysteine, and uric acid.[49] These phyla are thought to have a pro-inflammatory and oxidative stress effect in COPD. *H. influenzae*, which initially colonizes in the lower airways, can induce persistent infection or formation of biofilm. Biofilm acts as a bacterial reservoir, resulting in recurrent lower respiratory infection, microbial resistance, and immune escape.[50] Non-typeable *H. influenzae* is the most common type of bacteria in the respiratory tract of patients with COPD, and it metabolizes glucose via the respiratory-assisted fermentation pathway. This course induces increased secretion of end-products, such as acetate, formate, and succinate. These end-products act as immune metabolites locally at the site of infection and cause exacerbation of COPD.[51]

Current studies on microbial metabolism in COPD have been limited to the bacterial microbiome. Fungi and viruses are essential members of the airway microbial community, but few studies have reported them. Therefore, more extensive studies are required to fully characterize the role of airway microbial metabolism in the development of COPD.

Intestinal microbial metabolism

The intestinal and pulmonary mucosa share similarities in embryonic origin, physiological structure, and the immune response. Dysfunction of pulmonary gas exchange in COPD leads to visceral hypoxia and impairment of the intestinal barrier. In addition, this dysfunction exacerbates intestinal permeability, bacteria translocation, and endotoxin release, which further cause inflammatory immune activation. Pulmonary diseases are clinically accompanied by intestinal microbial dysbiosis and a deficiency in the immune response.[52] Intestinal microbes and their metabolites are thought to be involved in the pathogenesis of pulmonary diseases directly or indirectly.

A study that compared the fecal microbiome and metabolome between patients with COPD and healthy controls showed 146 different bacteria between these two groups. These bacteria included multiple

members of *Streptococcus*, *Streptococcus vestibularis*, and the *Trichophyton* family. These bacteria are associated with decreased lung function.[53] Additionally, intestinal Bacteroidaceae and Lachnospiraceae are increased after microbial transplantation or a high-fat diet. Some studies successively attenuated the symptoms of emphysema by suppressing local and systemic inflammation or altering the composition of intestinal microbes. This approach may provide a new paradigm for future therapy of COPD.[54]

Intestinal microbial metabolites can be transferred to the lungs via blood circulation.[55] Acetate, propionate, and butyrate are common short-chain fatty acids that are released into the bloodstream from the colon by bacterial fermentation of fibers. Short-chain fatty acids can then further modulate intrinsic pulmonary immunity. Dysfunction of absorption and digestion in the intestine occurs in patients with moderate to severe COPD. This dysfunction may induce a metabolic change in intestinal cells, which is accompanied by lower acetate concentrations in feces.[56] A study showed lower short-chain fatty acids concentrations in the colon in patients with COPD.[57] This study also showed decreased microbial abundance as well as diversity and increased harmful serum lipopolysaccharide concentrations in patients with COPD under the condition of 24 weeks of environmental particulate matter exposure.[57]

Overview of metabolic disorders in patients with COPD

Metabolic changes in COPD are complex and intricate. The onset and progression of diseases are regulated and affected by multiple factors. Lipid, amino acid, glucose, and nucleotide metabolism, as well as the metabolism of pulmonary and intestinal microbes, contribute synergistically to the pathogenesis of COPD in the form of a biological network. The immune system also plays a role in the pathogenesis of COPD by changing the course of metabolism in inflammatory cells and their capacity for the clearance of pathogens [Fig. 2].

When a person ingests food or nutrients, protein, lipid, glucose, and nucleotides are decomposed into small molecules after passing through the digestive tract, and are partially absorbed into the blood. Some non-absorbable substances, such as fiber, help excrete harmful substances from the intestine out of the body. The substances absorbed into the blood participate in energy metabolism in the body in the form of fatty acids, amino acids, glucose, and nucleotides. In healthy people, the process of catabolism and anabolism can maintain a dynamic balance. However, in people with COPD, the requirement for energy and substance synthesis greatly increases owing to the overwhelming consumption of COPD. The amount and proportion of small-molecule nutrient metabolites absorbed into the blood cannot meet the requirements for synthesis. As a result, required substances and energy are not synthesized, and harmful precursors also begin to accumulate. When nutrients in food pass through the intestinal mucosa, these nutrients simultaneously change the living environment of intestinal microbes by affecting the pH of the intestinal mucosal surface. Additionally, intestinal microbes directly act on the intestinal cells to increase their permeability and impair the efficiency of substance absorption. This process further causes reduced and disproportionate nutrient absorption into the blood and a disorder of nutrient metabolism in the body. In addition to the direct effect of metabolites on the intestinal mucosa, metabolites of microbes can also enter the blood stream to indirectly affect the lung mucosa and the immune barrier. Intestinal microbial metabolites can reach the lungs and attack the intrinsic immune mucosal barrier of the lungs, which further exacerbates the pulmonary symptoms of patients with COPD.

In summary, investigating methods to beneficially regulate lipids, amino acids, glucose, and nucleotide metabolism, as well as pulmonary and intestinal microbial metabolism, is essential in managing COPD. Studies have suggested that 30–60% of patients with COPD have malnutrition.[58] An insufficient or unbalanced intake of nutrients leads to a loss in the ability to offset excessive consumption during COPD. Dietary factors have been identified to play a role in preventing COPD. Antioxidant nutrients, vitamins, and fiber intake help to prevent and slow down the exacerbation of COPD. Eating more antioxidant-enriched food, such as vitamin C and retinol, can help prevent protease damage to lung tissue and protect the body from the development of disease.[59] A low-carbohydrate diet is also beneficial for patients with COPD.[59] Di-

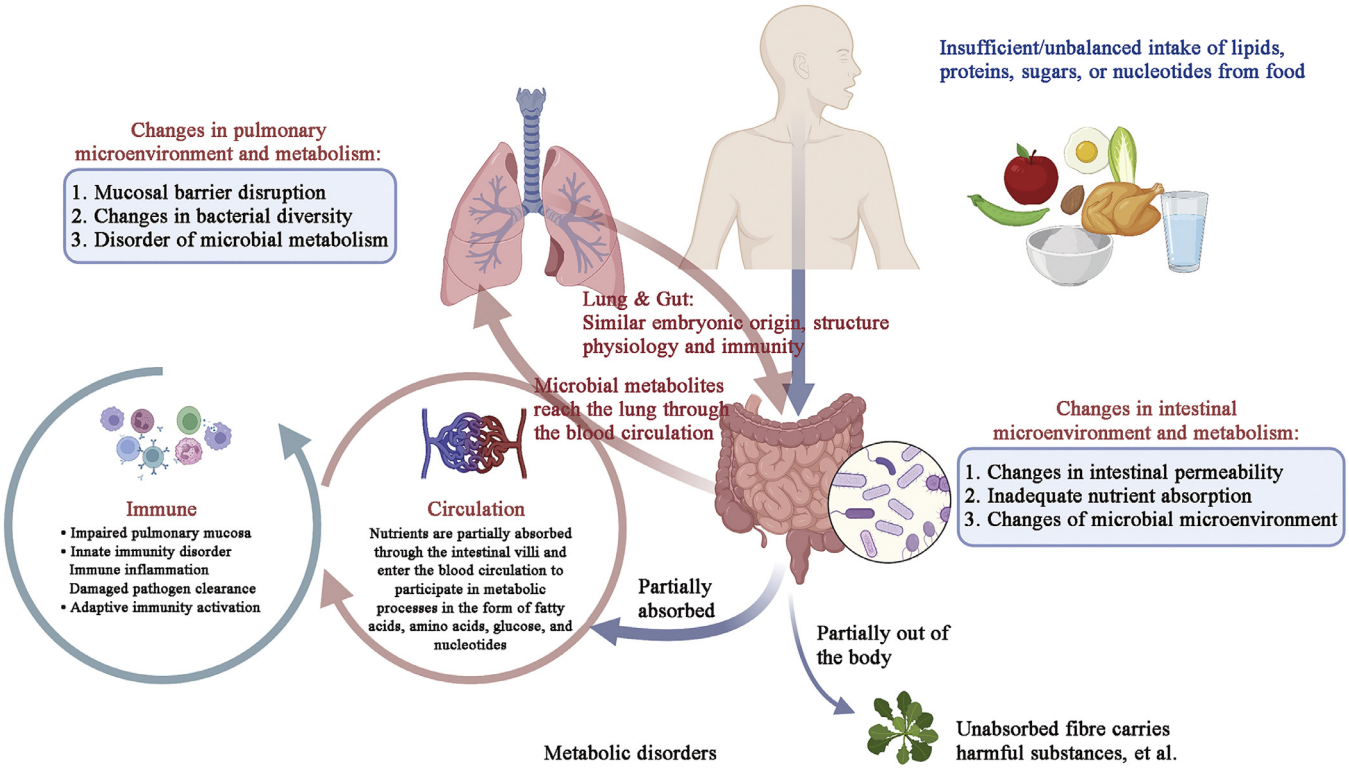

Fig. 2. Metabolic disorders in patients with COPD. COPD: Chronic obstructive pulmonary disease.

etary regulation prevents or suppresses respiratory infections by regulating the intestinal microenvironment, which is surprisingly effective in alleviating the symptoms of COPD. Dietary regulation appears to be the easiest method for managing COPD. Therefore, clinicians are encouraged to consider the potential effect of diet in improving the state of the lungs in COPD.[60] Intensified dietary management in COPD is a promising direction for the management of patients with COPD.

Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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