



Exploring the metabolomics and metagenomics of chronic obstructive pulmonary disease (COPD) and lung cancer: unraveling the complex interplay

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Abstract: Chronic obstructive pulmonary disease (COPD) and lung cancer are two leading respiratory disorders that impose substantial morbidity, mortality, and healthcare burdens worldwide. Epidemiological evidence indicates that patients with COPD have a significantly increased risk of developing lung cancer, suggesting potential shared pathophysiological mechanisms between these two conditions. Understanding the underlying molecular mechanisms of these diseases is crucial for the improvement of early detection, diagnosis, and treatment. In recent years, advances in high-throughput technologies have enabled the emergence of metabolomics and metagenomics as powerful tools in biomedical research. Metabolomics allows for the comprehensive profiling of small-molecule metabolites, providing a global snapshot of metabolic dysregulation associated with disease onset and progression. Concurrently, metagenomics facilitates an in-depth analysis of the microbial communities residing in the respiratory and gastrointestinal tracts, shedding light on the crucial roles of the microbiota in modulating host immunity, inflammation, and carcinogenesis. Metabolomics and metagenomics, cutting-edge fields in biomedical research, provide valuable insights into the intricate interplay between host genetics, environmental factors, and microbial communities. These two omics disciplines offer unique but complementary perspectives on the complex biological processes linking COPD and lung cancer. In this review, we delve into the recent research findings on altered metabolomics and metagenomics in COPD and lung cancer, while also exploring the possible associations between these two areas of study.

Keywords: Chronic obstructive pulmonary disease (COPD); lung cancer; metabolomics; metagenomics

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Introduction

Metabolomics involves the systematic study of small molecules, or metabolites, within a biological system (1).

These molecules represent the end products of various cellular processes and offer a comprehensive overview of the physiological state of cells and tissues. In the context of chronic obstructive pulmonary disease (COPD) and

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lung cancer, metabolomics has become an invaluable tool for identifying disease-specific metabolic signatures and potential biomarkers, shedding light on the mechanisms behind sickness, and paving the way for therapeutics development (2). Integrating metabolomic data with other omics datasets can offer a more holistic understanding of these intricate respiratory diseases (3).

Metabolic alterations in COPD

Metabolomic studies have revealed significant alterations in various metabolic pathways in COPD. One of the prominent findings is the dysregulation of lipid metabolism, characterized by elevated levels of free fatty acids, triglycerides, and ceramides. These changes are associated with systemic inflammation and oxidative stress in COPD patients. The research suggests that lipid dysregulation in AEC2 cells is a significant factor in enlarging alveolar spaces, with fatty acid synthase (FASN) being a potential therapeutic target for COPD (4). Recently, researchers have observed a reduction in both total pulmonary surfactant lipids and specific lipid species in patients with COPD (5). Reductions in total bronchoalveolar lavage (BAL) lipids, total phospholipids (PL), phosphatidylcholine (PC) 30:0, PC 32:0, and total cholesterol, among other lipids, are strongly correlated with the decline in lung function (6). Surfactant replacement treatment was found to enhance lung function in patients with stable bronchitis, a subtype of COPD, in a small-scale clinical experiment (7). Notwithstanding the noted amelioration, the underlying processes for this amelioration and the particular function of surfactant lipids in the regulation of lung function in COPD remain ambiguous (8). Additionally, muscle atrophy and systemic problems in COPD have been linked to changes in amino acid metabolism (AAM), particularly elevated levels of branched-chain amino acids (AAs) (9).

In many disorders, dysregulated lipid metabolism is a major factor. A previous study indicates that dysregulation of key lipid metabolic pathways plays a significant role in the pathogenesis of COPD (10). Previous research has shown that systemic dysregulation of lipid metabolism occurs in COPD, with heightened activity in the sphingolipid pathway observed in smokers with COPD compared to those without COPD (11). Several notable alterations have been detected in various blood lipid profiles. Certain researchers have reported diminished levels of serum or plasma sphingolipids in individuals with COPD, along with decreased concentrations of the aforementioned ceramide

in those who persistently smoke (12-14). Similarly, Gillenwater *et al.* reported that levels of both diglyceride and certain glycerophospholipids are diminished in patients, potentially serving as significant metabolic indicators of sex disparities in COPD (15). Other studies have also validated the diminished levels of PCs in affected patients (13,16).

Conversely, there seems to be an elevation in other glycerophospholipids and related molecules, including an increase in phosphocholine, a precursor to PC, as well as triglycerides (13,16-18). Liu *et al.*, employing lipidomics and statistical methods, also revealed changes, either elevated or decreased, in various PL, including four individual lipid molecules and ten lipid ratios that differentiate COPD from healthy lungs. Among these indicators, phosphatidylinositol (PI), PC, cholesterol ester (CE), and their ratios such as PI/CE and PC/CE, hold biological significance for COPD, as they are closely involved in pulmonary surfactant metabolism, inflammatory response, and lipid homeostasis, which are known to be dysregulated in COPD. These findings generated unique lipid signatures that hold promise as potential diagnostic biomarkers for COPD (19). Moreover, lysophosphatidylcholine acyltransferase 1 (LPCAT1) may represent a promising therapeutic target for COPD due to its critical role in pulmonary surfactant biosynthesis and PL remodeling (4). Additional validation studies with larger sample sizes may shed more light on the functions of these putative biomarkers in COPD diagnosis and treatment.

Furthermore, metabolites connected to the pentose phosphate pathway and the tricarboxylic acid cycle (TCA) have been found to be at different levels in COPD patients. A study suggests that dysregulation of plasma metabolites is associated with the phenotype of COPD (14). The results indicate that several AA levels were different in the COPD group compared to the non-COPD group. Particularly, glutamate and alpha-AAA were notably connected to emphysema in COPD. Particularly, metabolomic analysis revealed dysregulated sphingolipid and AAM in COPD patients, indicating potential involvement in disease pathogenesis. However, no significant correlation was observed between these elevated metabolites and FVC (20). Study indicates that significant alterations in metabolites derived from the arginine, transsulfuration, and folic acid pathways can serve as indicators of nitric oxide dysregulation and oxidative stress in COPD, as well as potential targets for novel therapeutics (21). These alterations may mirror an adaptive reaction to the heightened energy requirements linked with chronic inflammation and tissue repair

mechanisms, further investigation is required to elucidate the underlying mechanisms involved in the pathogenesis of COPD (22). Balgoma *et al.* found that serum levels of specific platelet acids produced from arachidonic acids and cytochrome P450 (CYP) oxidase derivatives were higher in COPD patients than in controls. Additionally, a decrease in lipoxygenase activity, which is responsible for converting fatty acids into leukotrienes, was observed (23). In COPD, monounsaturated fatty acids seem to be increased, but polyunsaturated fatty acids (PUFA) show a decrease (12,13,17). By using liquid chromatography-mass spectrometry, Berdyshev *et al.* found that lung tissue from patients with mild-to-moderate COPD had higher ceramide levels than that of control people. This was taken to mean that tissue had been destroyed. On the other hand, people who have severe airway blockage or lung function impairment had higher sphingolipid levels but lower ceramide levels (24). Critically sick patients' sputum included lower amounts of certain glycerophospholipid-related metabolites, as found by Zhu *et al.* This finding probably had an impact on the patients' levels of oxidative stress. The results showed a negative correlation with the levels of myeloperoxidase (MPO) and superoxide dismutase (SOD). SOD and MPO were shown to be differentially upregulated in moderate and severe COPD participants as compared to mild COPD/healthy subjects among the more than 500 metabolites that were investigated (25). Lung function has been linked to a number of lipids (fatty acids, glycerophospholipids, and sphingolipids), as well as different AAs and xenobiotics, according to research by Halper-Stromberg *et al.* Arginine, isoleucine, and serine were found to have the strongest correlation with FEV1/FVC among compounds generated from AAs (26). Additionally, AA-derived compounds, including leucine and lysine, were significantly associated with emphysema in a pattern in which decreased AAs were positively correlated with FEV1/FVC ratio and negatively with emphysema (26).

Metabolome of lung cancer

Metabolomics has been used in lung cancer to determine unique metabolic patterns linked to various subtypes and stages of the disease.

The "Warburg effect", which is characterized by an increased reliance on glycolysis for energy production even in the presence of oxygen, is one of the most startling findings (27). This metabolic shift is a hallmark of cancer cells and has potential implications for targeted therapies.

Affected metabolism of pentose phosphate and the TCA are two further metabolic abnormalities associated with lung cancer, increased levels of serine and glycine, and disruptions in lipid metabolism, particularly in PL and sphingolipid pathways (28-30). These metabolic alterations are frequently linked to treatment resistance, metastasis, and tumor growth. Studies revealed that lactate serves as a fuel for the TCA cycle in a mouse model of lung cancer and in human lung cancer patients. Furthermore, inhibiting lactate utilization through monocarboxylate transporter 1 (MCT1) inhibition resulted in the suppression of cell proliferation, observed in both lung cancer and colorectal cancer cells.

Guo *et al.* propose that single-nucleotide polymorphisms (SNPs) in the genes that code for important TCA cycle enzymes could potentially function as biomarkers for predicting outcomes in non-small cell lung cancer (NSCLC). The authors recommended further investigations involving diverse ethnic populations to validate the robustness of these potential biomarkers and confirm their broader clinical application (31). Lin *et al.* elucidated that the crucial role of fascin's glycolytic activity in enhancing the growth and metabolism of lung cancer (29). Their findings suggested that pharmacological inhibitors targeting fascin may hold therapeutic potential for treating lung cancer and maybe other cancers exhibiting fascin upregulation through reprogramming cancer metabolism (29). By combining weighted gene coexpression network analysis (WGCNA) with metabolomics, Ding *et al.* conducted an integrated analysis that revealed a strong correlation between poor glucose metabolism and the carcinogenesis of lung cancer. This finding suggested that glucose metabolism could be a target for lung cancer treatments (32). Pyruvate dehydrogenase kinases (PDKs) exert a pivotal role in coordinating the critical transition from cytoplasm-based glycolysis to mitochondria-based respiration, primarily by regulating the activity of pyruvate dehydrogenase (PDH). The up-regulation of PDKs significantly contributes to the Warburg effect observed in cancer cells, thereby serving as a promising therapeutic target for intervening cancer metabolism (33). Melatonin (MLT) was found by Chen *et al.* to inhibit the growth of lung cancer in the Lewis animal model. Likewise, they noticed that MLT inhibited the growth of A549, PC9, and LLC cells, which are lung cancer cells. Increased ATP synthesis, a higher ATP production-coupled oxygen consumption rate (OCR), higher ROS and mito-ROS levels, and a decrease in lactic acid secretion were all associated with these changes. MLT consequently greatly increased mitochondrial energy metabolism and

reversed the Warburg effect by increasing PDH activity via Sirt3 activation (34).

Misregulation of AAM is a significant factor that accelerates the development of cancer (35). Liu *et al.* measured the concentrations of 22 AAs in serum samples from 200 patients with NSCLC and 202 healthy controls (HCs) using liquid chromatography-tandem mass spectrometry (LC-MS/MS). Their findings suggested that pathways involving the metabolism of glycine (Gly), serine (Ser), threonine (Thr), alanine (Ala), aspartic acid (Asp), glutamic acid (Glu), and arginine (Arg) biosynthesis may play significant roles in the development of NSCLC (36). As technology continues to advance, metabolomics will provide more and more novel insight into lung cancer biology and contribute to development of new therapeutic strategies.

Lung microbiome and metagenomics in COPD

Lung microbiome in COPD

There is growing evidence that the lung has its own unique microbiome, and alterations in its composition and diversity are associated with COPD. In particular, increased abundance of potentially pathogenic bacteria, like *Streptococcus pneumoniae* and *Haemophilus influenzae*, has been detected in COPD patients' lower respiratory tracts. These microbial changes could be a factor in COPD exacerbations and chronic inflammation. The lung microbiome's functional potential, as revealed by metagenomics, has also been linked to COPD severity, through interacting with various molecular processes related to immunity, inflammation, and xenobiotic metabolism. Understanding the functional capacity of the lung microbiome is critical for deciphering its impact on COPD pathogenesis and progression.

Interest in the connection between intestinal health in COPD and the gut microbiota has grown recently, in especially with reference to the microbiota's capacity to control the levels of metabolites like propionate, butyrate, and acetate, or short-chain fatty acids (SCFAs) (37). Furthermore, butyrate produced by microbes in the gut can act as a hypoxic signal and improve the function of the epithelial barrier (37).

Interest in examining the putative relationship between the lung and gut microbiomes and their potential association with the etiology of COPD has developed as a result of the gut-lung axis hypothesis. The relationship between

the gut microbiome—measured by fecal samples—and the lung microbiome—measured by sputum, bronchoalveolar lavage fluid (BALF), or lung tissue—in relation to the pathophysiology of COPD has been the subject of recent studies (38,39). Sze *et al.* studied the microbiome in lung tissues from individuals with extremely severe COPD and compared it to that of patients with cystic fibrosis, smokers, and non-smokers without COPD. Their findings confirmed the link between the *Burkholderia* genus and the phylum Firmicutes in severe COPD, which is thought to be caused by an increased *Lactobacillus* abundance (40).

Additionally, according to research by Erb-Downward *et al.*, the geographical distribution of microbiota may have an effect on the variability of clinical outcome and disease severity (41). In a different investigation, Sze *et al.* found that samples taken from COPD patients had higher abundances of both Actinobacteria and Proteobacteria. The researchers emphasized that these variations were connected to the etiology and course of COPD (42). High concentrations of microorganisms in the lungs of patients with COPD may be linked to the onset and/or course of the illness (40). Research has confirmed that *Streptococcus* is one of the most prevalent genera among COPD patients. Microorganisms such as *Corynebacterium*, *Alloiococcus*, *Prevotella*, *Veillonella*, *Rothia*, *Neisseria*, and *Staphylococcus* are also commonly detected in patients with COPD (43).

Metagenomics in COPD

The study of microbial communities' aggregate genetic material is known as metagenomics, allowing researchers to characterize the composition and functional potential of these communities. The importance of the microbial community in our body, including the lungs, has been highlighted, with diverse bacterial genera such as *Prevotella*, *Veillonella*, and *Streptococcus* identified in healthy lung microbiomes (44-46). In relation to lung cancer and respiratory conditions like COPD, understanding the lung microbiome and its function in pulmonary disease has been made possible by metagenomics.

Previously culture-dependent molecular typing has identified important COPD-causing microbes and shown bacterial expansion in COPD lungs (47,48). In individuals with stable COPD, Hill *et al.* found a strong correlation between higher airway bacterial load and several indicators of inflammation. Together with albumin concentrations, these indicators include MPO, IL-8, leukotriene B₄, and leukocyte elastase (47). This finding underscores the

significant interactions between airway microbiota and immune components in individuals with stable COPD, nevertheless the interactions might be either direct or indirect. An important characteristic of COPD is co-infection or secondary infection. Because of the reduction of macrophage phagocytic function in a reactive oxygen species (ROS)-dependent manner, COPD patients are more likely than non-COPD patients to develop a co-infection or secondary bacterial infection (49). In COPD patients, the acquisition of novel bacterial infections such *H. influenzae*, *Moraxella catarrhalis*, and *S. pneumoniae* has been linked to acute exacerbations (48). Likewise, an elevated abundance of *Haemophilus* spp. has been linked to COPD exacerbation, as demonstrated by a long-term study of sputum samples' 16S rRNA sequencing (50). Furthermore, asthma exacerbations are often caused by rhinovirus infection, which can alter the structure of the respiratory microbiome by elevating the relative abundance of *H. influenzae* in COPD patients (51). Wang *et al.* have reported an increased adhesion of *H. influenzae* to nasal epithelial cells, potentially promoting secondary bacterial infections. In summary, species such as *Haemophilus* spp., *Moraxella* spp., and rhinovirus may contribute to exacerbation in a subset of patients with COPD and asthma (52). It is essential to validate these observed correlations in bigger cohorts or study comprehensively in animal models to discern how lung local microbiome interact with host immunity.

Lung microbiome and metagenomics in lung cancer

Lung microbiome in lung cancer

Unlike intestinal microbiota, microbiota in respiratory system has been poorly studied (53). According to early epidemiological statistics, pulmonary infections might aggravate up to 50–70% of cases of lung cancer during the course of the illness (54). Whereas metagenomic analyses have revealed the potential involvement of microbial genes in processes like DNA repair and drug metabolism. A study has reported alterations in microbiota composition in lung tumor tissue. For instance, the presence of certain bacteria, such as *Fusobacterium nucleatum*, has been associated with a pro-inflammatory state and poorer outcomes in lung cancer patients (55). Yan *et al.* showed that saliva samples from lung cancer patients had considerably greater concentrations of the oral bacteria *Veillonella* and *Capnocytophaga* (56). Similar to this, a number of other

bacterial taxa, such as *Proteobacteria*, *Granulicatella adiacens*, *Streptococcus*, *Streptococcus intermedius*, *Escherichia coli*, *Acinetobacter junii*, *S. viridans*, and *Streptococcus*, have also been connected to lung cancer (57–60).

Recently, numerous studies have demonstrated a strong association between local dysbiosis and lung cancer. The microbiota of lung tumors exhibited significantly lower taxonomic alpha diversity compared to non-malignant lung tissue samples (61). Although the specific consequences of altered bacterial diversity in lung cancer are not fully understood, previous studies suggest that increased alpha diversity is associated with better survival and treatment responses in cancers like cervical cancer and resected pancreatic adenocarcinoma.

The question is whether the local dysbiosis predisposes lung to malignant transformation, or the tumorous microenvironment triggers or exacerbates the loss of eubiosis. The exact cause-effect relationship between disturbed microbiota and carcinogenesis in lung remain unclear. In addition, local dysbiosis is suspected to be a crucial regulator for the response to cancer therapy (53). It has been demonstrated that post-obstructive pneumonia impairs both the overall survival of cancer patients and the effectiveness of lung cancer therapy, likely due to persistent airway inflammation, impaired drug delivery beyond the obstructed site, and increased risk of systemic infections (62).

Furthermore, the microbiota compositions were found to be correlated with cancer histopathology. According to reports, patients with metastases had increased levels of *Legionella* and the genus *Thermus* in their tumor tissues, suggesting a possible direct or indirect function for these bacteria in the development of cancer (51). *Veillonella* and *Megasphaera* were shown to be more prevalent in lung cancer patients' BAL samples by Sze *et al.* (40). This influence on outcomes is potentially mediated through the impact on the host immune response (55,56).

Metagenomics in lung cancer

Metagenomic investigations in lung cancer have concentrated on exploring the potential association between the lung microbiome and carcinogenesis. Traditionally it is deemed that there is a sterile environment in the lung. However, it has become increasingly clear in recent years that the healthy human lung is not sterile, as previously believed. Some recent studies have identified specific microbial signatures in lung cancer tissues, prompting inquiries into the microbiome's role in lung in tumor

development, progression, and the tumor microenvironment (63–66). By using deep shotgun metagenomic sequencing and fungi-enriched DNA extraction, Liu *et al.* discovered an enrichment of tumor-resident *Aspergillus sydowii* in lung adenocarcinoma (LUAD) patients. Their findings suggested that the intratumor mycobiome, despite its low biomass, plays a certain role in local environment, promoting or suppressing cancer cell growth. Targeting specific strains intratumorally may offer a potential avenue for improving therapeutic outcomes in patients with LUAD (67). In the tumor tissues of lung cancer patients, a meta-analysis showed a substantial drop in the *Proteobacteria* family Halomonadaceae and the species *Halomonas* (66). Another discovery was that lung cancer patients' fecal samples and tumor tissues had considerably lower relative abundances of the phylum *Actinobacteria* (68). However, this finding contrasts with the observations of Apopa *et al.*, who noted an elevated level of *Actinobacteria* in lung cancer tissue samples (69), this discrepancy may potentially be attributed to the limited sample size of the study and variations in the site of sampling.

Furthermore, in comparison to HCs, Hosgood *et al.* found that lung cancer patients' sputum samples had less variety while having higher relative abundances of *Granulicatella*, *Abiotrophia*, and *Streptococcus* (70). In a similar vein, *Streptococcus* was shown to be more abundant and less diverse in protective specimen brushing (PSB) samples from lung cancerous regions as compared to HCs (71). Additionally, lung cancer patients' saliva contained an enriched abundance of the family *Veillonellaceae* as well as the species *Veillonella*, *Capnocytophaga*, and *Selenomonas* (56). A study comparing lung cancer patients' BAL fluid samples to those with benign mass-like lesions revealed an enhanced abundance of the genera *Veillonella* and *Megasphaera* (72). The investigation of the respiratory microbiome for the clinical diagnosis and treatment of respiratory diseases is still in its early stages. However, insights gained from these studies could assist in microbial biomarker discovery, thereby aiding in the diagnosis of lung cancer.

Association between metabolomics and metagenomics in COPD and lung cancer

Studying the interplay between metabolomics and metagenomics in COPD and lung cancer is a somewhat unexplored but intriguing field of study. Integrated metabolomics and metagenomics offer complementary insights into the complex molecular networks driving

pulmonary diseases and lung cancer. In order to discover changed metabolites in both lung cancer and COPD, 30 serum samples from HC, 30 serum samples from lung cancer, and 30 serum samples from COPD were studied using a hybrid triple quadrupole-time of flight mass spectrometer (DI-ESI-QqQ-TOF-MS). A total of 35 metabolites, including AAs, fatty acids, lysophospholipids, PL, and triacylglycerides, were shown to be changed in both lung cancer and COPD. Among the most notable changes were those to the alanine, aspartate, and glutamate metabolic pathways (9).

Our knowledge of the human microbiome has improved thanks to next-generation sequencing (NGS) technology, which has made it possible to identify and characterize unculturable bacteria and predict their functions (57). A meta-analysis revealed that butyrate, homocysteine, and palmitate are microbial metabolites exhibiting robust interactions with host genes associated with COPD. In another *in vitro* study utilizing an emphysema mouse model, supplementation with acetate and propionate reached a notable therapeutic effect. Among these impacts were a decrease in the breakdown of alveoli and a rise in proinflammatory cytokines. Notably, propionate supplementation was specifically linked to a decrease in the CD3⁺CD4⁺IL-17⁺ T-cell population in both the lung and spleen. The findings underscore the therapeutic potential of acetate and propionate in the context of emphysema (59).

Metabolomics-metagenomics interactions in COPD & lung cancer

Recent studies have begun to explore how metabolic changes in COPD might be influenced by the lung microbiome. For example, Bacterial metabolism in the lung can generate metabolites that influence host immune activity and metabolism. SCFAs produced by some commensal bacteria, have been implicated in regulating inflammation, immune responses, and COPD pathogenesis (73). In other studies, the potential effect of propionate on the therapeutic response in lung cancer was suggested, as evidenced by its ability to induce apoptosis and cell cycle arrest via downregulation of Survivin and upregulation of p21 in lung cancer cell lines. Although these features resemble the action of senolytic agents, propionate has not been explicitly classified as a senolytic compound, and its effect may not be limited to senescent cells (60,61,63). Based on these observations, it is speculated that dietary and microbiome-derived SCFAs, including sodium propionate,

may be used as treatment supplementation. However, further *in vivo* research is needed to confirm the efficacy of SCFAs and sodium propionate in lung cancer treatment.

A nested case-control study was conducted to investigate the relationship between antibiotic usage and lung cancer risk, with a focus on the role of the resident microbiome in lung cancer progression. Compared to controls who were not exposed to antibiotics, those who had ten or more courses of antibiotics had a relative lung cancer risk of 2.52 (95% confidence interval, 2.25–2.83). This higher relative risk could be linked to inflammatory diseases brought on by recurrent infections and changes in the pulmonary microbiome in patients taking antibiotics (74). According to the concept, there are three different ways in which microbial imbalance, or dysbiosis, may contribute to the development of cancer: (I) disruption of immune equilibrium; (II) initiation of chronic inflammation; and (III) activation of cancer-promoting pathways (75–79). Firstly, dysbiosis has the potential to disturb the fundamental stimulation of the lung immune system. Microbial variety loss can affect how antigen-presenting cells are first activated, which can impede how well they respond to tumor antigens (80). On the other hand, excessive bacterial growth might cause the immune system to become overstimulated, which can cause the unchecked growth of CD4⁺ helper T (TH17) cells, which are known to be involved in the development of lung tumors and produce IL-17 (81). Secondly, the release of genotoxins and DNA-damaging compounds by commensal organisms is a key mechanism through which dysbiosis induces chronic inflammation. In addition to releasing ROS and reactive nitrogen species (RNS), dysbiosis-activated inflammatory cells can promote angiogenesis and carcinogenesis (62,82). Finally, a number of studies have demonstrated that specific microbiome species can directly activate pathways linked to the development of cancer.

Furthermore, the lung microbiome might influence the metabolism of drugs used in COPD treatment. Variations in microbial drug metabolism could impact drug efficacy and patient responses, emphasizing the importance of personalized therapeutic regimens that consider the interaction between host metabolism and lung microbiome. Interestingly, a study illustrated that inhibiting IL-6 substantially hindered the growth of lung cancer, resulting in decreased angiogenesis indicators, decreased tumor cell proliferation, and reduction of intrinsic STAT3 activity in tumor cells (83). As already stated, inflammation mediated by TH17 cells has been recognized as a crucial

factor in the development of lung tumors (84). Non-typeable *Haemophilus influenzae* (NTHi) has garnered significant interest due to its role in the pathophysiology of COPD. NTHi-induced COPD-like airway inflammation creates a tumor microenvironment conducive to cancer promotion and progression (85–87). The observation that individuals with COPD, a lung inflammatory condition, have a heightened risk of developing lung cancer persists even after adjusting for smoking status, implying an additional connection between lung cancer and extrinsic inflammation. Beyond the well-established association with cigarette smoke exposure, it is thought that bacterial colonization, particularly NTHi, plays a significant role, may cause airway inflammation in COPD patients (88). According to Jungnickel *et al.*, the tumor-promoting effects of bacteria like NTHi are mediated by the epithelial cytokine IL-17C via neutrophilic inflammation (89). Previously, studies have shown that NTHi-induced COPD-like airway inflammation promotes lung cancer in a K-ras-induced mouse model of airway conditions (88,90). The CCSPCre/LSL-K-rasG12D (CC-LR) mouse model, a K-ras mutant model of lung cancer, exhibits COPD-like airway inflammation upon exposure to an aerosolized NTHi lysate, which in turn promotes carcinogenesis. This finding was previously demonstrated by Velasco *et al.* Their investigation revealed that deletion of Toll-like receptors (TLRs) 2, 4, or 9 resulted in reduced angiogenesis, decreased tumor cell proliferation, and a lower tumor burden. This was accompanied by remodeling of the tumor microenvironment towards an antitumorigenic state and an increase in tumor cell death. Furthermore, these preliminary results were further validated and recapitulated in airway epithelial cells by the deletion of downstream signaling pathways, including MyD88/NF- κ B (91). Thus, NTHi may serve as a mediator between lung cancer and COPD. However, distinguishing between bacteria that actively promote cancer pathways and those that opportunistically colonize the tumor microenvironment remains challenging, despite promising research linking certain bacteria to carcinogenesis. In lung cancer, the interaction between host metabolism and the lung microbiome is another intriguing avenue of research. The metabolic preferences of cancer cells can shape/change the microbial community within the tumor microenvironment. For example, increased glycolysis in tumor cells can alter the availability of nutrients and metabolites that affect the growth and composition of the lung microbiome.

In lung chronic diseases, such as COPD, asthma, acute

exacerbation of chronic respiratory infection, and cancers, a decline in the diversity of microbes and dysbiosis has been frequently observed. This alteration in the lung microbiome can have direct or indirect implications for the onset and progression of lung cancer. While only a limited number of microbes are directly implicated in causing cancer, many play a complicit role in supporting cancer growth, often exerting their influence through the host's immune system (92). Acknowledging the lung's mucosal tissue composition hosting a diverse bacterial community, and acknowledging the frequent occurrence of pulmonary infections in patients with lung cancer, which significantly impact clinical outcomes, this research endeavors to unravel the relationship between local microbiota and inflammation associated with LUAD. The evidence presented in this research suggests that the activation of lung-resident $\gamma\delta$ T cells by local microbiota plays a pivotal role in provoking inflammation linked to LUAD. These results not only demonstrate a direct correlation between the emergence of lung cancers and the local microbiota-immune interaction, but they also pinpoint crucial cellular and molecular mediators that could be useful targets for lung cancer intervention (93). Liang *et al.* demonstrated that exosomes produced by lung cancer cells express tripartite motif-containing 59 (TRIM59), which can be transported to macrophages. This finding suggests that tumor-derived exosomal TRIM59 is essential for transforming macrophages into a tumor-promoting state by modulating the proteasomal degradation of ABHD5. The study also highlights that tumor-derived exosomal TRIM59 promotes lung metastasis by creating an inflammatory milieu and facilitating intercellular communication (94). Aerobic glycolysis is a metabolic characteristic commonly associated with activated dendritic cells (DCs); however, it is unclear how the glycolytic pathway and stimulator of interferon genes (STING) signaling interact with tumor-infiltrating DCs (95-97). Hu *et al.* have addressed this gap by demonstrating that glycolysis plays a pivotal role in driving STING signaling, thereby facilitating DC-mediated antitumor immune responses. Their study observed that glycolysis enhances STING-dependent DC activity in tissue samples obtained from patients with NSCLC. This research sheds light on the intricate relationship between metabolic processes, particularly glycolysis, and the STING signaling pathway, offering insights into the mechanisms underlying DC-mediated antitumor immune responses in the context of NSCLC (98). A study demonstrated that Gankyrin, a regulatory subunit of the 26S proteasome,

significantly exacerbates cancer-related characteristics in NSCLC, including increased cell viability, migration, invasion, and epithelial-mesenchymal transition (EMT). Conversely, Gankyrin suppression in NSCLC cells attenuates these malignant traits. The research also reveals that Gankyrin enhances and regulates YAP1 nuclear translocation and expression. YAP1 is notably involved in glycolysis, affecting glucose uptake, lactic acid production, and ATP generation, all of which contribute to Gankyrin's carcinogenic effects. Additionally, loss of YAP1 reversed the glycolysis upregulated by Gankyrin in NSCLC cells. Gankyrin knockdown was demonstrated to reduce YAP1 expression in a subcutaneous xenograft nude mouse model and to diminish carcinogenesis and EMT in A549 human LUAD cells (99-101). In conclusion, targeted inhibition of Gankyrin may provide a viable therapeutic approach for treating NSCLC. Both Gankyrin and YAP1 play critical roles in tumor metabolism (102). It is recognized that the cyclic GMP-AMP synthase (cGAS)-STING pathway plays a critical role in mediating the relationship between innate and adaptive immunity. Recent advances have broadened our understanding of its roles, encompassing not only general immunological processes but also its involvement in anti-tumor immunity and carcinogenesis. In the context of NSCLC, the loss of cGAS-STING signaling has been associated with heightened tumorigenicity and reduced infiltration of cytotoxic T lymphocytes. While this pathway is instrumental in mounting an anticancer response, a persistent and exaggerated cGAS-STING signaling can paradoxically contribute to the progression of certain inflammation-aggravated cancers (103-105). The cGAS plays a crucial role in recognizing cytoplasmic DNA. Upon DNA recognition, cGAS promotes the synthesis of cyclic GMP-AMP (cGAMP), which subsequently activates the STING. This activation leads to the expression of various proinflammatory cytokines and chemokines. Additionally, cGAS-STING signaling promotes the cross-presentation of DCs, initiating a tumor-specific CD8⁺ T cell response. This mechanism demonstrates significant potential in overcoming resistance and enhancing antitumor immunity, making it a promising avenue for therapeutic intervention (104). The activation of the pro-inflammatory nucleic acid-sensing pathway has been observed to trigger the Hippo pathway. Consequently, Yes-associated protein 1 (YAP1) and its paralog, transcriptional co-regulators with PDZ-binding motif (TAZ or WWTR1), are inactivated as a result of this activation. Subsequently, this leads to the suppression of tumorigenesis. In its active state, YAP

functions as a transcriptional driver, promoting the expression of immunosuppressive cytokines. This immune evasion strategy helps the cell evade immune surveillance and contributes to the development of preneoplastic conditions (103). Yang *et al.* identified a novel long non-coding RNA (lncRNA) named LINC02159 that exhibited upregulation in both tumor tissues and serum samples of NSCLC patients. The findings suggest that LINC02159 functions as an oncogenic factor in the progression of NSCLC by modulating ALYREF/YAP1 signaling. Moreover, the study indicates the potential utility of LINC02159 as a diagnostic marker and therapeutic target for NSCLC (106). Li *et al.* demonstrated that brain metastases show markedly downregulated levels of miR-596-3p, whereas primary NSCLC tumors exhibit increased expression of this miRNA. Target prediction analyses suggest that miR-596-3p regulates two critical genes involved in brain invasion: IL-8 and YAP1, which affect blood-brain barrier (BBB) permeability and inhibit cancer cell invasion, respectively. These findings suggest that miR-596-3p plays a crucial role in NSCLC brain metastasis through its modulation of the YAP1-IL8 network. This newly discovered miRNA-mRNA axis represents a potential therapeutic target for the management of NSCLC brain metastasis (107). Wei *et al.* suggest that both miR-550a-3-5p and YAP1 could potentially serve as novel targets for controlling brain metastasis. This indicates that the modulation of these factors may hold promise as a therapeutic strategy for managing or preventing the spread of cancer to the brain. Identifying and targeting specific molecules involved in the process of brain metastasis could be crucial for developing effective treatment approaches (108). Similarly, in small cell lung cancer (SCLC), YAP1 has been identified as a key player in various biological functions. This includes its involvement in cell proliferation, drug sensitivity, EMT, and neuroendocrine differentiation. The role of YAP1 in these processes highlights its significance in the molecular mechanisms underlying the progression and characteristics of SCLC (109,110). Evidence has been mounting that the Hippo-YAP1 signaling pathway is essential for preserving lung tissue homeostasis, with its dysregulation being implicated in tumorigenesis. YAP1/TAZ, through physical interaction with TEAD transcription factors, exerts oncogenic activities via transcriptional regulation. In solid tumors, the Hippo-YAP1 pathway interacts with various signaling pathways, including Wnt/ β -catenin, the receptor tyrosine kinase cascade, Notch, and TGF- β , synergistically contributing to

tumorigenesis (111-113). A comprehensive understanding of the regulatory mechanisms governing the Hippo-YAP1 pathway in tumorigenesis is believed to provide novel insights for accurate therapeutic interventions.

The possible role of physical interaction with TEAD transcription factors has also been shown by metagenomic research to exert oncogenic activities via transcriptional regulation. In solid tumors, the Hippo-YAP1 pathway interacts with microbiome-associated signaling pathways to modulate host immune responses. Certain bacteria may trigger pro-inflammatory pathways or immune evasion strategies that impact the tumor microenvironment. Understanding these interactions could provide new avenues for therapeutic intervention and immunomodulation in lung cancer.

Conclusions

Metabolomics and metagenomics are powerful tools that have deepened our understanding of the molecular intricacies of COPD and lung cancer. These fields have uncovered unique metabolic signatures and microbial profiles associated with each disease, shedding light on potential biomarkers and therapeutic targets. Furthermore, the interaction between host metabolism and the lung microbiome is the subject of new study that could lead to the discovery of novel diagnostic pathways, treatment, and personalized medicine. Integrating metagenomics and metabolomics techniques could help us comprehend the intricate relationships between COPD and lung cancer in greater detail, ultimately leading to improved patient outcomes and novel therapeutic strategies.

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