Review Article

Microbiota dysbiosis in lung cancer: evidence of association and potential mechanisms

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Abstract: Over the past decade, revolution in microbial research has provided valuable insights into the function of microbes that inhabit human body. This complex community of microbes, collectively named as microbiota, displays tremendous interaction with a host to maintain homeostasis of the local environment. Lungs were even previously regarded as sterile for a long time. With the development of high-throughput next-generation sequencing technology, a low-density, diversified microbial ecosystem is found in bronchoalveolar lavage fluid, sputum, and lung tissues. Current research confirms that, compared with healthy people, patients with lung cancer show changes in the relative abundance of multiple genera. Emerging evidence has suggested that dysbiosis of the lung microbiota may play a critical role in lung carcinogenesis by affecting metabolic, inflammatory pathways and immune response. We briefly summarize the relationship between lung microbiome and lung cancer and discuss the potential mechanisms mediating lung microbiota and lung cancer. Thus, we provide innovative strategies for early prevention and personalized treatment of lung cancer.

Keywords: Dysbiosis; lung microbiome; lung cancer

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Introduction

Human body is inhabited by trillions of microbes (i.e., bacteria, archaea, fungi, protists, and viruses) that are increasingly considered critical to human health (1,2). Symbiotic communities in our bodies are involved in degradation of nutrients, fight against invasion by xenobiotics, elimination of pathogens, and maturation of our immune system (3). Restrained by the development of experimental methods and technology, our knowledge of this vast microbiome seems to be very limited previously. With the development and spread of sequencing technology, we have gained a deep understanding of the human microbiome; thus, our understanding of the role of microbiome in human health and disease has greatly increased (4,5). On the basis of the key features of the microbiome including microbial diversity, relative abundance, and microbial gene richness, human microbiome project consortium studies have demonstrated that healthy individuals have high bacterial diversity and

distinct individual variability at the species level (6,7). Recent studies have illustrated complex interaction between the human microbiome and different disease statuses, including cancers (8-11). For example, *Helicobacter pylori*, a common *Proteobacteria* residing in the upper gastrointestinal tract, significantly increases the risk of gastric cancer and pancreatic carcinogenesis (12,13). Furthermore, *Enterotoxigenic Bacteroides fragilis*, as one of the most prevalent pathobionts detected in colorectal cancer patients, has been shown to induce murine colon tumorigenesis by generating DNA mutagens, such as the genotoxin, superoxide, and hydrogen peroxide (14). In addition to the studies that focus on single pathogenic species, increasing studies have identified changes in the composition of microbiota in various anatomic sites associated with carcinogenesis (15). Furthermore, hard evidence suggests that physiological and environmental factors including diet, smoking, alcohol consumption, and air pollution significantly alter the composition of microbiota in various anatomic sites (16). These factors are often associated with carcinogenesis. Thus, extensive studies are required to further identify the link between microbiota and cancer development. Lung cancer, as the leading cause of cancer-related deaths worldwide in men and women, shows an increase in incidence in developing countries (17). It has a grim prognosis, that is, over half of people diagnosed with lung cancer die within one year of diagnosis, and the five-year survival rate is less than 18% (18). The two main histological groups of lung cancer are small cell lung carcinoma (SCLC, 15% of all lung cancers) and non-small cell lung carcinoma (NSCLC, 85% of all lung cancers). NSCLC is further classified into squamous cell carcinoma, adenocarcinoma, and large cell carcinoma (19). Although well characterized in etiology, morphology, and intrinsic molecular character, little is known about the relationship of lung cancer with the lung microbiota. In this review, we mainly summarize the current research progress of the lung microbiota and the role of lung microbiome in various lung diseases and other related diseases, especially in lung cancer. In addition, we focus on the change in lung microbiome and the potential pathogenic mechanisms to provide a theoretical basis for treating this deadly disease.

Lung microbiota in healthy humans and lung diseases

Although lungs are connected with outside air, the lungs of healthy people were even previously regarded as sterile for a long time. Recently, a great number of studies confirm the presence of lung microbiota in healthy people. Culture-independent molecular techniques were used in previous studies to analyze the most common bacterial phyla including *Bacteroidetes*, *Firmicutes*, and *Proteobacteria*, and the prominent genera include *Prevotella*, *Veillonella*, and *Streptococcus* (20-23). These genera are also detected in oral samples. Furthermore, lungs contain specific bacteria such as *Enterobacteriaceae*, *Haemophilus*, *Methylobacterium*, *Ralstonia*, and *Tropheryma* species (21,24). In healthy lungs, microbial density is low, containing 10^3 cells/g to 10^5 cells/g of tissue (for comparison, intestinal microbiota reaches a density of 10^{11} to 10^{12} cells/g) (25,26). The composition of lung microbiota is determined by the balance between microbial immigration from the upper respiratory tract and microbe elimination (e.g., by coughing or immune defenses), with relatively few contributions from regional growth of the microbes themselves (27-29). Microbial immigration from the upper respiratory tract occurs mainly through microaspiration. This view can be supported by the high similarity between the lower airway and oropharynx microbiota rather than nasopharynx. Microaspiration is a passive process involving the oral and pharyngeal muscles; it mainly occurs during sleep (8). Nevertheless, a study using 16S rRNA gene sequencing shows similarity of the lung microbiota to the oropharynx and nasopharynx microbiota in young children (23). This finding might be due to the different anatomical structure of upper respiratory tract in children and adults. The balance between microbial immigration (e.g., via microaspiration) and microbial elimination (e.g., mucociliary clearance, cough, and host immune defenses) determines the composition of the lung microbiota.

Furthermore, another layer of complexity is added by the impact of environmental conditions (e.g., pH, temperature, nutrient, oxygen tension, and activation of host inflammatory cells) on this process. Thus, the geographical, physiological, and immunological diversities also shape the composition of the lung microbiota (30,31). Recent studies have indicated that the atmospheric concentration ($\mu g/m^3$) of particulate matter with diameters of 10 and 2.5 micrometers (PM10 and PM2.5) might affect the lung microbiota and respiratory functions (32-34). In addition, household air pollution plays a role in the composition of lung microbiome (35,36). Smoking, as the risk factor for lung diseases, has been reported to alter microbial diversities and communities in the lower respiratory tract of mice and human trials (37,38). Antibiotic is another important

factor influencing lung microbiota; it has attracted a great deal of attention in recent years. However, the influence of antibiotics on microbiota is mainly focused on intestinal trials; less is known about the influence on lung microbiome composition (39-41). A recent study has shown that after one year of azithromycin treatment, bacterial diversity decreased in patients with asthma (42). Similarly, treatment with azithromycin reduced alpha diversity in patients with chronic obstructive pulmonary disease (COPD), but did not change the total bacterial burden (43).

In patients with lung disease, the balance between immigration and elimination is disturbed. Thus, the lung microbiota is altered, the abundance of symbiotic bacteria is decreased, and pathogenic bacteria predominate. This change leads to a decrease in diversity of lung microbiota and is associated with the progression of chronic lung diseases, such as COPD (44-54), cystic fibrosis (55-58), asthma (59-62), and idiopathic pulmonary fibrosis (63-65) (*Table 1*).

In summary, homeostasis of the lung microbiota is associated with the balance between immune defense of pathogens and immune tolerance of the commensals. On one hand, host lungs have established three major pathways to defend against the invasion of pathogens. First, Mucus, mainly secreted by goblet and club cells, provides an effective defense against epithelial injury and limits the migration of pathogens to epithelial cells. Thus, the systematic spread of microbes in the body is prevented; inflammation is also prevented, and homeostasis of the microbiota and host is protected (66,67). Second, alveolar surfactant containing sIgA covers the surface of lung alveolar epithelial cells and participates in lung innate immunity (68). Finally, the epithelial cell layer is not only a structural barrier, but also a component of the innate host defense. Epithelial cells express several pattern recognition receptors (PRRs) and secrete antimicrobial molecules and mucins to defend against invading pathogens (69). The PRRs, including toll-like receptor (TLR) and nucleotide-binding oligomerization domain-like receptors can prevent the overload of pathogens or metabolites by identifying pathogen-associated molecular patterns or cell damage-associated molecular patterns (70,71). Then, the pathogens are further eliminated by activating the downstream inflammatory signaling pathway (72). On the other hand, immune tolerance of commensals is regulated by anti-inflammatory macrophages in alveoli by inhibiting inflammatory pathways and adaptive immune responses (73,74).

Relationship between gut microbiome and lung microbiome

Recently, many studies have begun to focus on the two-way manner between gut and lungs, which is known as the "gut–lung axis" (75). This theory is based on "gut–lymph" theory of Samuelson *et al.* (76). According to the theory, many macrophages and other immune cells are present in the intestinal submucosa or the mesenteric lymph nodes that contain many translocating bacteria. If they are not cleared by the first line of defense, then the surviving bacteria, cell wall fragments, or protein fragments of dead bacteria would escape along with the cytokines and chemokines produced in the intestine and travel along the mesenteric lymphatic system to the cisterna chyli and then into the circulatory system. One way is access to pulmonary circulation, leading to local activation of dendritic cells and macrophages and the initiation and differentiation of T cells. Another way is activation of immune cells, which affect the lung area through their own migration, in the first contact with the antigen in the intestinal mucosa. Therefore, gut microbiomes influence the lung microbiome partly through inhalations of the gastroesophageal content, swallowing of the sputum, and most importantly through modulation of host immune.

Studies have shown that cigarette smoke, as a crucial risk of COPD, can also change the composition of intestinal microbiota and reduce the diversity of intestinal bacteria (77), and the change in composition of microbiota is closely related to many inflammatory diseases, including intestinal inflammation and inflammatory bowel disease (IBD) (75,78,79). Many respiratory infections are often accompanied by gastrointestinal symptoms given that the "gut–lung axis" is bidirectional (80). This finding has also been demonstrated in animal models with respiratory infection (81,82). However, direct evidence for the influence of lung microbiota and its products and their circulation is lacking. An animal experiment showed that nonabsorbable tracer deposited into the nasal cavity can be found in the gastrointestinal tract subsequently (83). Further research is needed to validate and extend these findings.

Microbiome and lung cancer

Oral microbiome and lung cancer

The oral microbiome is highly correlated with the lung microbiome because lungs are directly connected with the oral cavity. More recently, the association of oral

Table 1 Current findings on relationship between lung microbiota and non-oncology lung

Disease	Reference	Sample	Method	Significant outcome
COPD	Erb-Downward JR *et al*. (44)	BALF/lung tissue	16S rRNA	significant abundance of *Pseudomonas* and *Haemophilus*
	Hilty *et al*. (45)	Oropharynx/ Bronchoscopy	16S rRNA	significant increases in *Pathogenic Proteobacteria*, particularly *Haemophilus* spp.
	Kim *et al*. (46)	Lung tissue	16S rRNA	significant increases in *Firmicutes*, particularly *Lactobacillales; Ochrobactrum* was only found in the COPD
	Sze *et al*. (47)	Lung tissue	16S rRNA	significant abundance of *Firmicutes*, particularly *Lactobacillales*
	Pragman *et al*. (48)	BALF	16S rRNA	The dominant phyla: *Actinobacteria* and *Proteobacteria* in moderate COPD; *Actinobacteria* and *Firmicutes* in severe COPD; Increased the genus in *Nocardioides* and *Balneimonas;* Decreased the genus in *Humicoccus* and *Thermoactinomyces*
	Millares *et al*. (49)	Sputum	16S rRNA/ bacterial culture	The dominant phyla: *Proteobacteria* and *Firmicutes, Actinobacteria, Bacteroidetes* and *Fusobacteria*; Increased the genus in *Streptococcus, Pseudomonas, Moraxella, Haemophilus, Neisseria, Achromobacter* and *Corynebacterium*
	Garcia-Nuñez *et al*. (50)	Sputum	16S rRNA/ bacterial culture	The dominant phyla: *Proteobacteria* and *Firmicutes,* followed by *Actinobacteria*; relative abundance of the genera *Rothia, Streptococcus*, and *Veillonella*
	Lee *et al*. (51)	Sputum	16S rRNA	The dominant phyla: *Proteobacteria, Bacteroidetes* and *Firmicutes;* more abundant of the genera *Haemophilus, Neisseria, Fusobacterium, Prevotella,* and *Porphyromonas* in severe COPD, more abundant of the genera *Propionibacterium, Bacillus, Pseudomonas, Escherichia* and *Porphyromonas* in moderate COPD
	Mayhew *et al*. (52)	Sputum	16S rRNA	The dominant phyla: *Firmicutes, Proteobacteria* and *Bacteroidetes*; the most abundant genera: *Veillonella, Haemophilus, Streptococcus, Prevotella* and *Moraxella*
	Jubinville *et al*. (53)	Sputum	16S rRNA	The dominant phyla: *Firmicutes, Proteobacteria* and *Bacteroidetes*; the dominant genera: *Streptococcus, Prevotella, Moraxella* and *Veillonella*
	Leitao Filho *et al*. (54)	Sputum	16S rRNA	The dominant phyla: *Firmicutes, Actinobacteria, Bacteroidetes, Proteobacteria* and *Fusobacteria;* the dominant genera: *Streptococcus, Prevotella, Haemophilus, Rothia, Veillonella* and *Pseudomonas*
CF	Feigelman *et al*. (55)	Sputum	16S rRNA	Increased abundance of *Pseudomonas, Staphylococcus, Stenotrophomonas*, and *Achromobacter*
	Frayman *et al*. (56)	BALF	16S rRNA	The dominant phyla: *Firmicutes, Proteobacteria, Actinobacteria, Bacteroidetes* and *Fusobacteria*
	Laguna *et al*. (57)	BALF	16S rRNA	Increased abundance of *Pseudomonas, Staphylococcus, Haemophilus, Stenotrophomonas* and *Achromobacter*
	Carmody *et al*. (58)	Sputum	16S rRNA	Increased abundance of *Streptococcus, Fusobacterium, Veillonella, Prevotella, Gemella* and *Rothia*

Table 1 (*continued*)

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Disease	Reference	Sample	Method	Significant outcome
Asthma	Durack *et al*. (59)	Bronchoscopy	16S rRNA	Increased abundance of *Haemophilus, Neisseria, Fusobacterium, Porphyromonas* and *Sphingomonodaceae*; decreased in *Mogibacteriaceae* and *Lactobacillales*
	Teo *et al*. (60)	NP	16S rRNA	The dominant phyla: *Proteobacteria, Firmicutes, Actinobacteria*, *Bacteroidetes* and *Fusobacteria;* the dominant genera: *Moraxella*, *Streptococcus, Corynebacterium, Staphylococcus, Haemophilus* and *Alloiococcus*
	Huang *et al*. (61)	Bronchoscopy	16S rRNA	The dominant phyla: *Bacteroidetes* and *Firmicutes*; Increased abundance of *Actinobacteria* in severe asthma
	Marri *et al*. (62)	Sputum	16S rRNA	The dominant phyla: *Firmicutes*, *Proteobacteria*, *Actinobacteria*, *Fusobacterium* and *Bacteroidetes*
IPF	Molyneaux *et al*. (63)	BALF	16S rRNA	The dominant phyla: *Firmicutes*, *Proteobacteria*, *Bacteroidetes* and *Actinobacteria*; Increased abundance of *Campylobacter* and Stenotrophomonas in AE-IPF; *Veillonella* in the stable IPF
	Han *et al*. (64)	BALF	16S rRNA	Increased abundance of *Staphylococcus* and *Streptococcus*
	Molyneaux *et al*. (65)	BALF	16S rRNA	Increased abundance of *Haemophilus, Streptococcus, Neisseria* and *Veillonella*

COPD, chronic obstructive pulmonary disease; CF, cystic fibrosis; IPF, idiopathic pulmonary fibrosis; BALF, bronchoalveolar lavage fluid; NP, nasopharyngeal.

microbiome with lung cancer has received considerable attention. Several prospective cohorts have consistently shown that periodontal diseases, known to alter the oral microbiota, are associated with increased lung cancer risk after controlling potential confounding factors including smoking (84-88). 16S rRNA gene sequencing results of salivary microbiome suggest an elevated abundance of *Capnocytophaga and Veillonella* with a reduced number of *Neisseria* (89). Another study in nonsmoking female with lung cancer indicates that genera *Blastomonas and Sphingomonas* were significantly increased in the oral microbiota of patients with lung cancer, whereas *Acinetobacter and Streptococcus* were higher in controls (90). Although the association between periodontal disease and lung cancer is generally considered strong, the causality remains a large problem, and further research is needed to evaluate potential mechanisms.

Lung microbiome and lung cancer

Studies have shown that patients with lung cancer may have similar lung microecology. A summary overview of the relationship between lung microbiota and lung cancer is shown in *Table 2* (30,91-102). Hasegawa *et al.* collected intraoperative bronchial fluids using a microsampling probe from nine subjects with pulmonary carcinoma and cultured anaerobically on blood agar plates. Predominant isolates from intraoperative bronchial fluids are commonly indigenous to the oral cavity, namely, *Streptococcus*, *Veillonella*, *Gemella*, *Porphyromonas*, *Olsenella*, and *Eikenella*. These findings indicate that intraoperative bronchial fluids contain bacteria probably derived from the oral microbiota (93). The result of another study on airway brushing samples showed that the prominent phyla or genera were also dominated in oral samples of patients with lung cancer (94). Simon *et al.* collected sputum samples from 10 patients with possible LC, four of which were eventually diagnosed with LC (LC+), and six had no LC after one year (LC–). Among the seven bacterial species found in all samples, *Streptococcus viridans* was significantly higher in LC+. Among the five species having significantly higher abundances in LC+, *Granulicatella adiacens* showed the highest level of abundance change. Moreover, *G. adiacens* abundance was correlated with six other bacterial species only in LC+ samples, namely, *Enterococcus sp. 130*, *Streptococcus intermedius*, *Escherichia coli*, *S. viridans*,

Table 2 Current findings on relationship between lung microbiota and lung cancer

Reference	Study participants	Sample	Method	Significant outcome
Cameron *et al.* (91)	LC+ [4], LC– [6]	Sputum	16S rRNA	Increased *G. adiacens*; *Enterococcus sp. 130, Streptococcus intermedius, Escherichia coli, Streptococcus viridans, Acinetobacter junii*, and *Streptococcus sp. 6.*
Lee *et al.* (92)	LC+ [20] Benign diseases [8]	BALF	16S rRNA	Increased two phyla (*Firmicutes* and *TM7*) and four genera (*Veillonella, Megasphaera, Atopobium*, and *Selenomonas*)
Hasegawa *et al.* (93)	LC+ [10]	BALF	16S rRNA	Dominated by *Streptococcus, Veillonella, Gemella, Porphyromonas, Olsenella* and *Eikenella*
Yu *et al.* (30)	LC [165]	Lung tissue	16S rRNA	Dominated by *Proteobacteria*; Increased the genus *Thermus* in advanced stage patients; Increased *Legionella* in develop metastases patients
Liu *et al.* (94)	LC+ [24] healthy control [18]	Bronchoscopy	16S rRNA	Decreases in microbial diversity; Increased the genus *Streptococcus* and *Neisseria*; Decreases *Staphylococcus* and *Dialister* gradually from healthy to noncancerous to cancerous site
Zhuang *et al.* (95)	LC [30] healthy control [30]	Faeces	16S rRNA	The composition (beta diversity) differed significantly between patients and controls; Decreases the bacterial phylum *Actinobacteria* and genus *Bifidobacterium*; Increased *Enterococcus*
Zhang *et al.* (96)	NSCLC [39], healthy control [20]	Saliva	16S rRNA	Increased the phylum *Firmicutes* and its two genera *Veillonella* and *Streptococcus*; Decreases the relative abundances of *Fusobacterium*, *Prevotella*, *Bacteroides* and *Faecalibacterium*
Greathouse *et al.* (97)	LC+ [143], LC– [33]	Lung tissue	16S rRNA	Increase in richness and alpha diversity; Increased the phylum *Proteobacteria* and decreased *Firmicutes*; Increased the abundance of *Acidovorax* and *Klebsiella* in smokers
Apopa *et al.* (98)	LUAD [11], LUSC [8] adjacent normal samples [8]	Lung tissue	16S rRNA	Increased four phyla (*Proteobacteria*, *Bacteroidetes*, *Actinobacteria*, and *Firmicutes*); Increased phylum *Cyanobacteria* in LUAD samples
Peters *et al.* (99)	NSCLC [19]	Lung tissue	16S rRNA	Tumor tissue had lower richness and diversity; Increased the family *Veillonellaceae*; Decreases the genus *Cloacibacterium*, and family *Erysipelotrichaceae*
Tsay *et al.* (100)	LC+ (39), disease control (36), healthy control [10]	Lower airway samples	16S rRNA	Increased *Prevotella*, *Streptococcus* and *Veillonella*
Hosgood *et al.* (101)	Never smoking female LC [8], never smoking female controls [8]	Sputum/buccal samples	16S rRNA	Increased *Granulicatella*, *Abiotrophia* and *Streptococcus* in sputum; Increased the Bacilli species (*Streptococcus infantis* and *Streptococcus anginosus*) in sputum

Table 2 (*continued*)

Table 2 (*continued*)

Reference	Study participants	Sample	Method	Significant outcome
Bingula *et al.* (102)	Forty NSCLC	Saliva/faeces/BALF	16S rRNA	4 main phyla are found in both lung and intestinal microbiota (*Firmicutes*, *Bacteroidetes*, *Actinobacteria*, and *Proteobacteria*)

BALF, bronchoalveolar lavage fluid.

Acinetobacter junii, and *Streptococcus sp. 6* that could be related to LC stage. The results in this study showed that the spontaneous sputum would be a viable source of bacterial biomarkers for LC status and stage (91). Another study on sputum samples from a nonsmoking female patient with LC showed the enrichment of *Granulicatella*, *Abiotrophia*, and *Streptococcus* (92). Lee *et al.* studied bronchoalveolar lavage fluid from 28 patients and found that *Acteroidetes*, *Firmicutes*, and *Proteobacteria* were the most common phyla, and *Prevotella*, *Streptococcus*, and *Neisseria* were the most common genera in both groups. The relative abundance of two phyla (*Firmicutes* and *TM7*) and four genera (*Veillonella*, *Megasphaera*, *Atopobium*, and *Selenomonas*) were significantly increased in patients with lung cancer. Furthermore, the combination of the two genera (*Veillonella* and *Megasphaera*) showed a higher receiver operating characteristic value than the individual genus in predicting lung cancer. Thus, this combination could be used as biomarker for lung cancer. Another noteworthy finding was that smoking patients with lung cancer have a significantly higher ratio of *Firmicutes* to *Bacteroidetes* than nonsmoking patients (92). A similar result is also shown in a study of lung tissue samples with COPD (47). In addition, an increase in the phylum *TM7* was reported in COPD (48). These results further support the view about the strong relationship between COPD and lung cancer, as indicated in other studies (103,104).

Most previous studies on lung microbiota used oral, sputum, or bronchoscopic brushing samples. A common concern with these samples is that they may be contaminated by the upper respiratory or oral microbiota. Some studies have suggested that the bacteria in lung carcinogenesis may be associated with aspiration of oral or pharyngeal bacteria. However, a research on 165 nonmalignant lung tissue samples from cancer patients showed that the lung microbiota has distinct features that differ from those of the oral cavity and other body sites. In fact, it is dominated by *Proteobacteria*. Similar results from other studies show the domination of *Proteobacteria* in lung tissue samples with lung cancer (97,98,102). Furthermore, the genus *Thermus* is more abundant in tissue from advanced stage patients, and *Legionella* is high in patients with metastases (30). Moreover, the lung microbiota is affected by exposure to air pollution and tobacco smoking.

In summary, patients with lung cancer show changes in the relative abundance of multiple genera. Consistent conclusions from all recent studies are limited due to the small sample size of most studies and the heterogeneity of lung cancer. However, most studies indicate that *Streptococcus* and *Proteobacteria* may be the key bacteria of lung cancer. Nevertheless, further large-scale studies are needed to verify certain microbial biomarkers for patients with lung cancer.

Possible mechanisms mediating lung microbiota and lung cancer

Dysbiosis of the microbiome is mainly manifested by the decrease in symbiotic bacteria and the increase in pathogenic bacteria, and then inducement of carcinogenesis at multiple levels, including metabolism alteration, inflammation, and immune response (105,106). Present studies on the mechanisms of microbiota and cancer are mainly focused on intestinal flora and colon cancer (107-109). When dysregulated, the intestinal microbiota can contribute to colorectal cancer development through the modulation of immune function and the production of microbial-derived metabolites (110). The increase in pathogenic bacteria can lead to chronic inflammation through the persistent generation of inflammatory mediators, thereby affecting cell apoptosis and increasing mutations. Moreover, the metabolites of bacteria, such as reactive oxygen and nitrogen, through direct DNA damage or modification of cellular signaling generate a pro-carcinogenic environment. Bacteria influence cellular signaling and/or induce mucosal inflammation to initiate or promote colon tumorigenesis through producing a variety of oncogenic toxins to directly

damage DNA(111).

However, studies on the mechanism of lung microbiota and lung cancer are few. Great effort is exerted to identify and characterize a potential causal relationship from the lung cancer and lung microbe interaction.

A large cohort study by Boursi *et al.* demonstrated that recurrent exposure to certain antibiotics (penicillin, cephalosporins, or macrolides) may increase lung cancer risk (112). Antibiotic-induced dysbiosis not only alter bacterial abundance, composition, and diversity in animal models, but also accelerate Lewis LC that progressed on the host side (113). The dysbiosis of lung microbiota may promote the development of lung cancer by releasing cancer-promoting bacterial metabolites and inducting host inflammatory pathways (114). The possible mechanisms mediating lung microbiota and lung cancer are illustrated in *Figure 1*.

Metabolism

Recent studies have implicated that the metabolites of bacteria may be involved in the development of lung cancer. Cytolethal distending toxin (CDT) as a bacterial genotoxin produced by variety of gram-negative bacteria, such as *Actinobacillus*, can induce apoptosis in human lung adenocarcinoma A549 cell line (115). *G. adiacens* was found to be associated with lung cancer. In addition, the research on functional capacity demonstrated that *G. adiacens* was involved in the metabolism of polyamine (91). Interestingly, elevated levels of polyamines, such as putrescine and gamma-aminobutyric acid, have been associated with a range of cancers including lung malignancies (116). Apopa *et al.* found that the abundance of *Cyanobacteria* was significantly increased in lung adenocarcinoma, and the functional analysis suggested that the *Cyanobacteria* toxin (i.e., microcystin) might be related to the increase in procyclic acidic repetitive protein 1 (PARP1), thereby enhancing inflammation and leading to cancer. The result was further confirmed in microcystin-challenged lung adenocarcinoma (A427) cell lines (98).

In addition, some bacteria in the intestinal microbiome can increase the bioavailability of anticancer drugs. Niu suggested that *Bacteroidaceae* and *Prevotellaceae* contain species capable of hydrolyzing ginsenosides present in red ginseng extract (RGE), enhancing the effect of RGE in the prevention and treatment of lung cancer (117). This finding indicates that the decrease in symbiotic bacteria could accelerate LC progression.

Inflammatory pathways and immune response

In recent years, considerable studies have shown that chronic inflammation plays an important role in the development of several forms of cancer, including lung cancer. Dysbiosis of the microbiota can activate the inflammatory pathway to trigger the proliferation and survival of epithelial cells under certain conditions, promoting the development of tumors. TLR4, as a member of pattern recognition receptor, initiates natural immunity in the early stage of pathogen invasion. Increasing evidence shows that it plays a crucial role in the development of tumor microenvironment and has been increasingly investigated. TLRs promote carcinogenic effects by activating nuclear factor κB (NF-κB) pathway, releasing inflammatory factor, and activating transcription 3 (STAT3) (118). TLR4 is expressed more strongly in lung cancer tissue than in paracancer tissue (119).

Ochoa *et al.* found that exposure of the airway to smoke particulates and nontypeable *Haemophilus influenzae* (NTHi) promoted lung cancer cell proliferation by release of IL-6 and TNF, which further activated the STAT3 and NF-kB pathways in airway epithelium (120). Another study demonstrated that IL-6 blockade significantly inhibited lung cancer promotion, tumor cell intrinsic STAT3 activation, tumor cell proliferation, and angiogenesis markers (121).

In addition, Th17 cell-mediated inflammation has been identified to play a critical role in lung tumorigenesis (122). Jungnickel *et al.* indicated that the epithelial cytokine IL-17C mediates the tumor-promoting effect of bacteria, such as NTHi, through neutrophilic inflammation (123). Recently, growing awareness of the importance of NTHi in the pathophysiology of COPD has been observed, and COPD-like airway inflammation induced by NTHi provides a tumor microenvironment that favors lung tumor promotion and progression (124-126). Thus, NTHi may act as a bridge between COPD and lung cancer.

Furthermore, accumulating evidence indicated that upregulation of the PI3K pathway played a central role in the cell proliferation, survival, and tissue invasion of early lung cancer (127). Tsay *et al.* reported that the oral taxa (*Streptococcus* and *Veillonella*) enriched in the lower airways of patients with lung cancer were associated with upregulation of the ERK and PI3K signaling pathways, and the same signaling pathways were upregulated *in vitro* exposure of airway epithelial cells to *Veillonella*, *Prevotella*, and *Streptococcus* (128). These studies preliminarily indicated that pulmonary bacteria up-regulate the expression of inflammatory mediators and cytokines by acting on

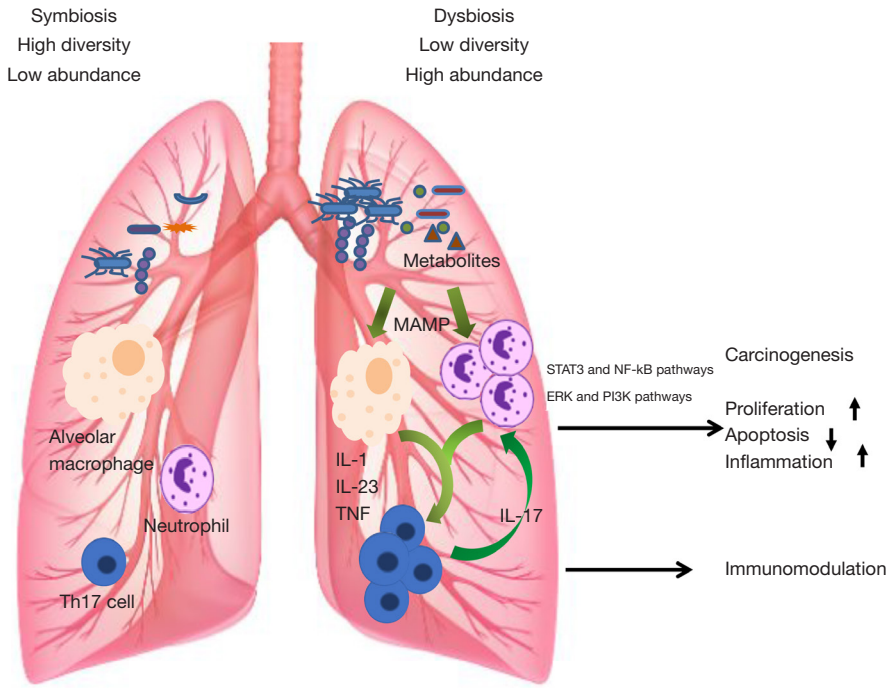

Figure 1 Possible mechanisms mediating lung microbiota and lung cancer. The commensal microbiota contributes to immune tolerance through decreasing lung inflammation and dendritic cell recruitment. Macrophages and T cells respond to microbial colonization and prevent the overload of pathogens or metabolites (left panel). When the balance is disturbed, pathogens or metabolites up-regulate the expression of inflammatory mediators and cytokines (e.g., IL-1, IL-23, TNF, and IL-17) by acting on MAMP. These inflammatory mediators or cytokines trigger downstream critical signaling pathways (e.g., STAT3 and NF-kB pathways and ERK and PI3K pathways), which promote the carcinogenesis of the host cells.

microbe-associated molecular pattern recognition receptors (MAMP), thereby affecting the development of lung cancer.

Application of lung microbiome in clinical trial

Most experimental studies analyzing the application of lung microbiota in the clinical therapy mainly focused on animal models. The relevant content theme has been covered in several reviews (11,129,130). Most commonly studied microorganisms in the context of lung disease are known probiotics, such as *Lactobacillus* and *Bifidobacterium*. Their beneficial role in animal models of lung diseases has been well demonstrated (130). For instance, orally or intranasal administered *Lactobacillus* and *Bifidobacterium* were shown to protect mice against lung infection by augmenting antibody production, enhancing natural killer cell activity, and IFN-γ production, as well as increasing secretion of IL-10. In addition, *Lactobacillus* and *Bifidobacterium* were shown to confer beneficial effects on allergic airway inflammation by inducing T_{reg} cells and T_H1 cells. Currently, experimental studies on the application of lung microbiome in lung cancer are relatively limited. Orally administered *Lactobacillus acidophilus* on mice lung cancer model was shown to reduce tumor size and increase survival rate after receiving cisplatin treatment (131). Moreover, administered *Enterococcus hirae* and *Barnesiella intestinihominis* in combination with chemoimmunotherapy can significantly improve efficacy in patients with advanced lung cancer (132).

Conclusions

In summary, accumulating evidence for specific bacteria as biomarkers of lung cancer presence is found. However, the precise mechanism of lung microbiota on the regulation of lung cancer is still partly unclear. Future research of the causal role of these bacteria in lung carcinogenesis will be beneficial for our understanding of the interactions between the lung microbiota and lung function, which is also

valuable in ultimately providing therapeutic targets for lung cancer prevention and therapy.

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Footnote

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