Insight into microbial extracellular vesicles as key communication materials and their clinical implications for lung cancer (Review)

JEONG YUN JANG[1*], JI HOON SEO[2*], JAE JUN CHOI[3], HYUN JIN RYU[4,5], HYUNJUN YUN[6], DONG MYEONG HA[7] and JINHO YANG[7]

[1]Department of Radiation Oncology, Konkuk University Medical Center, Konkuk University School of Medicine, Seoul 05030, Republic of Korea; [2]Department of Environmental Health, Korea University, Seoul 02841, Republic of Korea; [3]Department of Fire Disaster Prevention, Graduate School of Semyung University, Jecheon, Chungcheongbuk-do 27136, Republic of Korea; [4]Department of Endocrinology and Metabolism, Kyung Hee University College of Medicine, Seoul 02447, Republic of Korea; [5]School of Medicine, Kyung Hee University Hospital at Gangdong, Seoul 05278, Republic of Korea; [6]The AI Convergence Appliance Research Center, Korea Electronics Technology Institute, Gwangju 61011, Republic of Korea; [7]Department of Occupational Health and Safety, Semyung University, Jecheon, Chungcheongbuk-do 27136, Republic of Korea

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Abstract. The complexity of lung cancer, driven by multifactorial causes such as genetic, environmental and lifestyle factors, underscores the necessity for tailored treatment strategies informed by recent advancements. Studies highlight a significant association between the lung microbiome and lung cancer, with dysbiosis potentially contributing to disease development via inflammation, immune response alterations and bacterial metabolite production. Furthermore, exposure to airborne bacteria may influence lung health by introducing pathogenic species or altering the human microbiome, thereby implicating certain dominant airborne bacteria in lung diseases, including the exacerbation of lung cancer. Extracellular vesicles (EVs) facilitate cell-to-cell communication, penetrating mucosal barriers to impact various organs, notably the lung. Epidemiological evidence suggests a strong relationship between the presence of microbial EVs (MEVs) in the air and chronic pulmonary diseases, with indications of a potential risk for lung cancer. MEVs play a significant role in pulmonary disease development by inducing airway inflammation and affecting lung function. The microbiome and MEVs offer considerable potential as novel tools in precision medicine for lung cancer. Biological data analysis and artificial intelligence technology advancements are pivotal for fully realizing their diagnostic and therapeutic capabilities. These developments can potentially shape the future landscape of lung cancer diagnostics, therapeutics and prevention strategies.

Correspondence to: Professor Jinho Yang, Department of Occupational Health and Safety, Semyung University, 65 Semyung-ro, Jecheon, Chungcheongbuk-do 27136, Republic of Korea
E-mail: iamjinho@semyung.ac.kr

*Contributed equally

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1. Introduction

Lung cancer is the most newly diagnosed cancer worldwide, comprising 12.4% (2.48 million cases) of cases and causing 18.7% (1.82 million deaths) of cancer-associated mortalities, and it is now the leading concern among males, with an incidence rate of 15.3% (1.57 million cases), surpassing prostate cancer in 2022 (1). In addition, domestic cancer statistics in South Korea demonstrate the highest fatality rates, with crude mortality rates of 36.8 per 100,000 individuals (18,902 deaths) in 2021, aligning with international trends (2). While lung cancer is traditionally classified into non-small cell lung cancer and small cell lung cancer, recent advancements such as next-generation sequencing (NGS) have revealed a significant heterogeneity within the disease. This has led to the identification of various pathological subtypes, highlighting the complexity of lung cancer and underscoring the need for tailored treatment strategies for individual patients (3-5).

Well-known risk factors for lung cancer include genetic polymorphisms, tobacco smoking, diet, alcohol consumption, chronic inflammation, exposure to ionizing radiation and occupational exposure to substances such as asbestos, chromium compounds, silica and diesel exhaust (6). Similar to most types of cancer, lung cancer is recognized to result from the interplay of various multifactorial causes. Among these factors, the microbiome has also emerged as a topic of growing interest in research (7). In the past, it was believed that the lung was sterile; however, recent research has uncovered a range of commensal microbiomes, including fungi, bacteria and viruses, all of which contribute to homeostasis (8,9). Numerous studies have investigated the association between these microbiomes and various lung diseases, including cancer (10). Although dysbiosis is not exclusively associated with cancer development, it has been found to correlate with innate immunity, suggesting potential therapeutic implications (11-13). Therefore, the present review aims to summarize the research on the influence of both human and environmental microbiomes on the occurrence and progression of lung cancer, as well as their potential clinical implications.

2. Association between the microbiome and lung cancer

Human microbiome. Multiple studies have highlighted significant associations between lung cancer and the human microbiome using fecal, sputum, tissue and saliva samples, as summarized in Table I. The lung microbiota is shaped by interactions with the gut and oral microbiome, as well as external exposures (14). In patients with lung cancer, Streptococcus was consistently found at higher levels in sputum, tissue and saliva compared to healthy individuals (15-17), while its abundance was significantly reduced in fecal samples (18). Conversely, *Faecalibacterium*, which is typically abundant in feces, was found in higher levels in fecal samples from patients with lung cancer but reduced in their saliva (17-19). Other pro-inflammatory bacteria, such as *Ruminococcus* and *Klebsiella*, were also elevated in fecal samples of patients with lung cancer compared to healthy controls (18,20). By contrast, beneficial genera such as *Bifidobacterium* and *Bacteroides* were observed in greater abundance in fecal samples from healthy individuals (19,21,22).

In addition to comparisons with healthy controls, studies have also evaluated differences in microbiota composition between patients with lung cancer and those with benign pulmonary conditions or other cancer types. For instance, higher levels of *Veillonella*, *Megasphaera*, *Atopobium* and *Selenomonas* were reported in patients with lung cancer compared to individuals with benign lung lesions (23). Similarly, *Haemophilus* levels showed significant variability between lung cancer and patients with esophageal squamous cell carcinoma (20). These findings suggest that the lung microbiota may interact with bacteria originating from the oral cavity or pharynx, further emphasizing the concept of a gut-lung axis (14).

Despite these advances, variability in study outcomes remains a challenge, often attributed to small sample sizes, diverse cancer subtypes, and differences in patient characteristics, such as age, sex and medical history. Furthermore, discrepancies arise from variations in sequencing approaches and taxonomic databases. For example, targeting different 16S ribosomal RNA regions (such as V1-V3 vs. V3-V4) and using different platforms, such as Illumina MiSeq and Roche 454, yield differing results. Additionally, inconsistencies across databases [such as SILVA (https://www.arb-silva.de/), Ribosomal Database Project (RDP interface is no longer available), Greengenes (https://greengenes2.ucsd.edu/) and National Center for Biotechnology Information (https://www.ncbi.nlm.nih.gov/)] contribute to the variability (24-26). Nonetheless, several studies have consistently identified *Streptococcus* and *Faecalibacterium* as key genera associated with lung cancer, with the former being particularly prominent (14,17).

Dysbiosis, characterized by a shift in the microbiome that favors harmful over beneficial bacteria, plays a central role in cancer progression. It promotes inflammation, alters metabolic pathways and dysregulates immune responses, as observed in studies of colorectal cancer (14,27,28). In the lung, similar mechanisms are suspected but remain underexplored. Emerging evidence suggests that dysbiosis of the lung microbiota may facilitate lung cancer progression through bacterial metabolite release and activation of inflammatory pathways (29). Moreover, the gut-lung axis, influenced by gut microbiota such as *Lactobacillus reuteri* and *Clostridium*, shapes immune responses in the lungs, highlighting its potential role in lung cancer pathogenesis (30,31). Despite these findings, large-scale studies are needed to validate microbial biomarkers for lung cancer, which could pave the way for novel diagnostic and therapeutic strategies.

Environmental microbiome. A previous study investigated the relationship between environmental microorganisms and human health (Fig. 1). Humans are exposed to environmental microorganisms through the air, food, soil and water, which circulate and interact, influencing various ecological systems (32). These microbes can infiltrate the body via respiration, skin contact and ingestion, integrating into the complex interactions of these ecosystems. Subsequently, environmental microorganisms that have penetrated the body can directly impact human health by introducing pathogenic bacteria or indirectly by altering the human microbiome (33,34).

In particular, pulmonary diseases are related to exposure to airborne bacteria. Previous studies have identified some prevalent airborne bacteria, revealing that their composition varies depending on the characteristics of the outdoor environments. In outdoor air, the dominant genera varied according to meteorological conditions (32). In the indoor air of an office, the most dominant genera were *Methylobacterium*, *Enterobacteriaceae_unidentified genus*, *Exiguobacteirum* and *Bacteroides* (32). Also, Shin *et al* (35) reported that Micrococcus, Paracoccus, Staphylococcus and Enhydrobacter were the common genera in indoor air of childcare facilities.

Several studies have elucidated that airborne microbes are associated with lung diseases (36-40). Exposure to airborne microbes has been implicated in developing and exacerbating lung diseases, such as asthma and chronic obstructive pulmonary disease (COPD) (36). For example, *Pseudomonas aeruginosa* is common in patients with cystic fibrosis and COPD (37). It is known that exposure to bioaerosols, such as allergens, toxins and pro-inflammatory agents, induces airway inflammation, leading to respiratory symptoms (38). Asthma and bioaerosol

Table I. Clinical studies on microbiome genera alteration in lung cancer compared with healthy individuals and other lung diseases using 16S ribosomal RNA method.

	Microbiome		
Sample	Increase	Decrease	(Refs.)
Feces	*Haemophilus, Faecalibacterium*	*Neisseria, Fusobacterium, Treponema, Rothia, Burkholderia, Filifactor, Dialister, Mycoplasma, Catonella, Anaerovorax, Acholeplasma, Bacteroides, Peptococcus, Megamonas, Bradyrhizobium, TG5*	(19)
	Eubacterium, Ruminococcus, Faecalibacterium	*Streptococcus, Enterococcus, Roseburia*	(18)
	Klebsiella, Streptococcus	*Haemophilus*	(20)
	Enterococcus	*Bifidobacterium*	(21)
		Lachnospira	(124)
	Ruminococcus	*Faecalibacterium, Streptococcus, Bifidobacterium, Veillonella*	(22)
Sputum	*Parabacteroides, Eggerthella, Weissella*	*Haemophilus, Dialister, Burkholderia, WAL_1855D, Neisseria, Bulleidia*	(19)
	Granulicatella, Abiotrophia, Streptococcus,	*Sphinogomonas, Leptotrichia*	(15)
Tissue	*Streptococcus*	*Staphylococcus*	(16)
		Corynebacterium, Halomonas, Lachnoanaerobaculum,	(125)
		Acidovorax	(126)
Saliva	*Veillonella, Streptococcus*	*Fusobacterium, Prevotella, Bacteroides, Faecalibacterium*	(17)

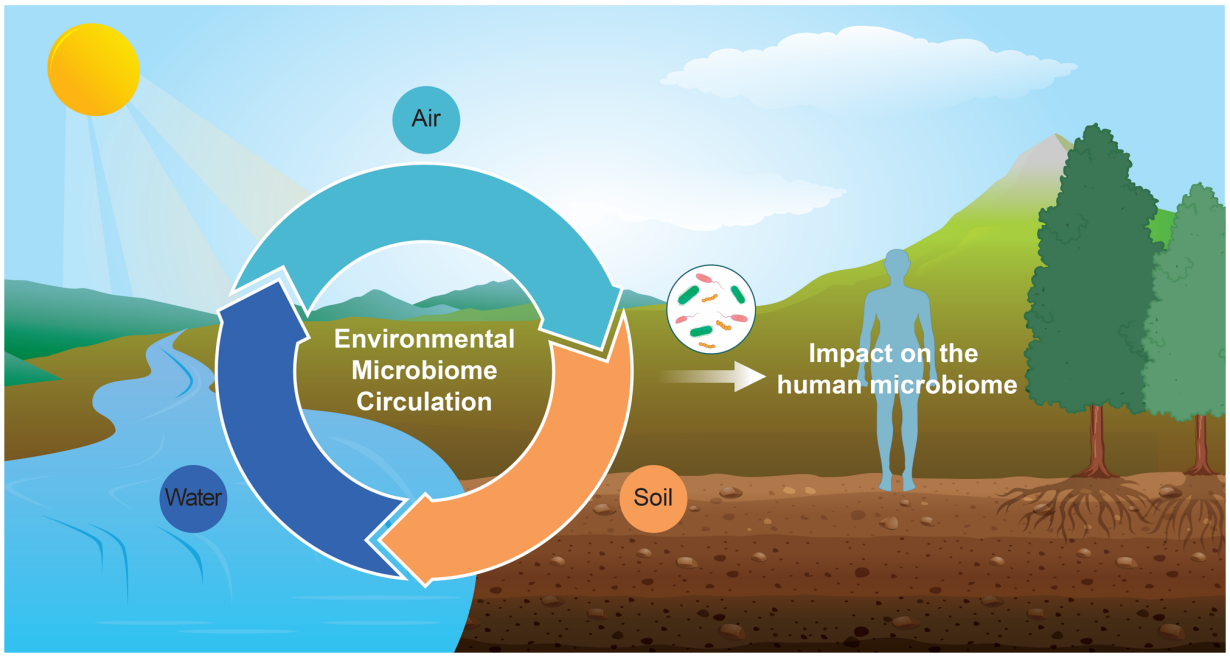

Figure 1. Relationship between the microbiomes of the environment and humans. Environmental microbiomes, circulating through air, water and soil, come into contact with humans, subsequently impacting the human microbiome.

exposure have been found to reduce lung function while increasing pulmonary inflammation (39). This series of lung function decline, increased inflammation and dysregulation can contribute to the development of lung cancer. Additionally, a study reported a relationship between exposure to bioaerosols and the development of specific cancers, including pancreatic,

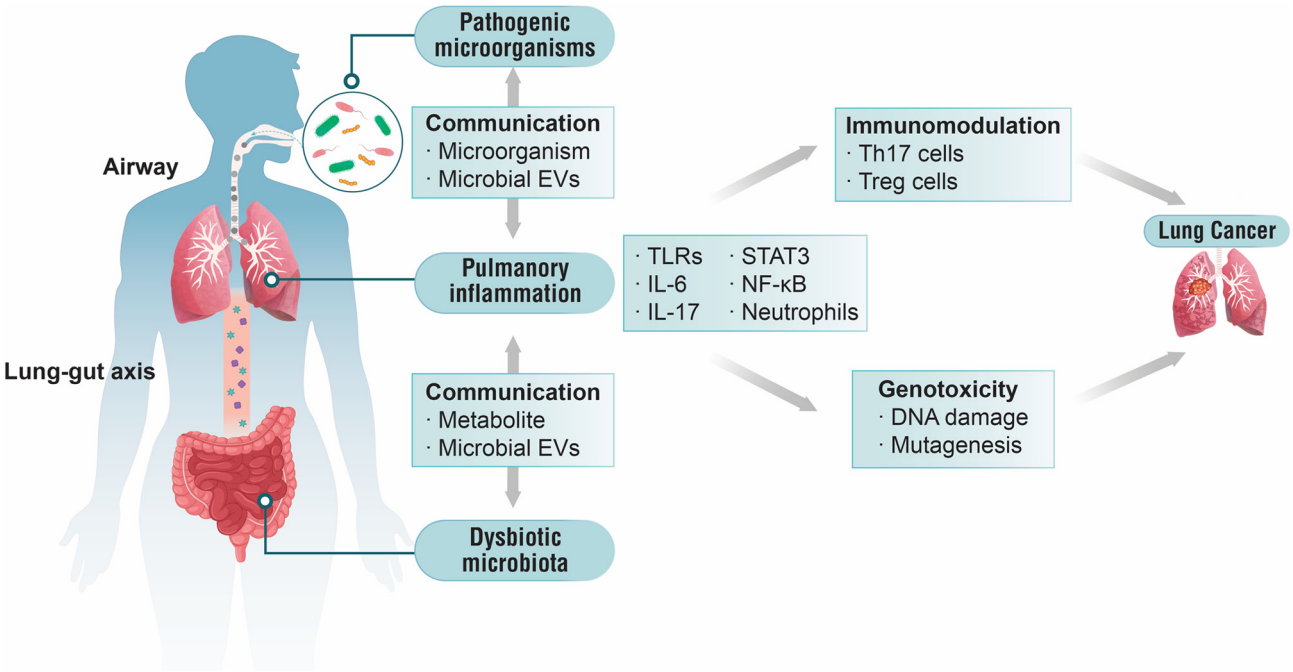

Figure 2. Microbiome as a significant factor in lung cancer carcinogenesis. Environmental microorganisms and gut microbiome contribute to pulmonary inflammation, which can lead to development of lung cancer. EVs, extracellular vesicles; TLRs, Toll-like receptors; Th, T helper cells; Treg, regulatory T cells.

liver and lung cancer (40). In summary, alterations in the pulmonary micro-environment and functions, which may contribute to the development of lung cancer, are increasingly acknowledged; however, research into the definitive impact of the microbiome on its pathogenesis remains limited.

3. Microbial extracellular vesicles as key communication materials between the microbiome and lung cancer

Exposure to microbial extracellular vesicles. Extracellular vehicles (EVs) are cell-to-cell communication materials enclosed in a lipid bilayer containing proteins, lipopolysaccharides (LPS) and nucleic acids, ranging from 20 to 200 nm in diameter. Microbial EVs (MEVs), found in all bacteria, are known as outer membrane vesicles (OMVs) in Gram-negative bacteria and membrane vesicles (MVs) in Gram-positive bacteria (41,42). Gut commensal microbes secrete MEVs, which penetrate the mucosal barrier and circulate throughout the body, reaching organs such as the lung, liver and skeletal muscle after oral administration (43). Additionally, dietary habits influence the microbiome and MEV composition, impacting human health and disease risk (44-46). For example, the microbial diversity in the feces of individuals on habitual Western diets was decreased compared with plant-based diets (44). Nanosized particles, including MEVs, are absorbed through inhalation and spread to various organs. These particles can accumulate in deep lung tissue, potentially affecting lung function over time (47).

Epidemiological studies have linked MEVs in indoor dust with chronic pulmonary diseases. A clinical study found that 63.6% of children with asthma had IgG1 sensitization to MEVs in indoor dust, suggesting a role in chronic lung diseases (48). Higher levels of anti-dust EV IgG antibodies were observed in patients with asthma, COPD and lung cancer compared to healthy controls (49,50). In summary, while research is in its early stages, MEVs may pose a significant risk for lung disease, including cancer.

Pathogenesis of microbial extracellular vesicles in the development of lung diseases. As the EV membrane is embedded with surface ligands that interact with receptors on target cells, EVs can attach to and modify the physiological state of recipient cells (51,52). Furthermore, MEVs have recently been shown to be involved in the development of a wide variety of diseases, including cancer (24,53).

MEVs in beds were found to be mainly derived from pathogenic bacteria, such as *Pseudomonas*, *Acinetobacter*, *Enterobacter* and *Staphylococcus* (50). The prolonged exposure to MEVs in inhaled indoor dust induces significant airway inflammation, leading to severe asthma-like responses as well as emphysema. The induction of emphysema is of particular concern, as it is known to be a major factor in the development of irreversible airway obstruction (48). The exposure to MEVs during respiration and dysbiosis of gut microbiota constitute two primary pathophysiological mechanisms-the airway and gut-lung axis-contributing to disease development (Fig. 2).

When the parent cell is an extracellular gram-negative bacterium, OMVs induce T helper (Th)17 responses, leading to neutrophilic inflammation via the release of IL-17. This inflammation often causes airway hyperreactivity, fibrosis and conditions such as asthma and COPD, which may elevate the risk of lung cancer (54). A previous study has shown that OMVs from *Escherichia coli* trigger IL-17A-dependent neutrophilic inflammation and emphysema in mice, accompanied by elastase upregulation (55). Intraperitoneal injection of *E. coli* EVs induces lung dysfunction and mortality (56). Similarly, *P. aeruginosa* EVs exacerbate pulmonary inflammation through Toll-like receptor (TLR)2 and TLR4 activation, elevating in the

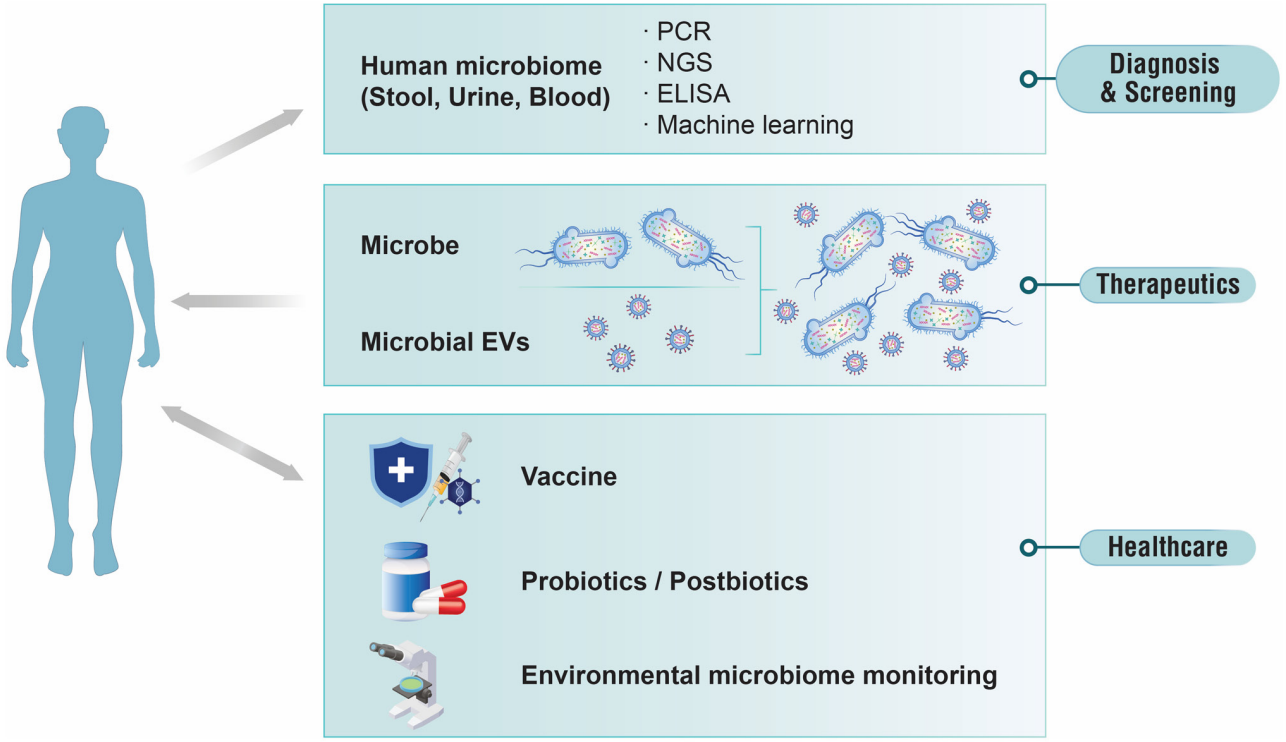

Figure 3. Clinical applicability of the microbiome: i) Diagnosis, including screening; ii) therapeutics; and iii) healthcare, such as monitoring and supplements. NGS, next generation sequencing; EVs, extracellular vesicles.

chemokines (CXCL1 and C-C motif ligand 2) and the cytokines (IL-1β, TNF-α, IL-6 and IFN-γ), alongside neutrophil and macrophage infiltration (37). Moreover, indoor dust, including various bacterial components, has been associated with both Th1 and Th17 responses, leading to the induction of neutrophilic pulmonary inflammation (48,57). By contrast, MVs from intracellular Gram-positive bacteria primarily induce Th1 polarization via IFN-γ, leading to mononuclear inflammation and alveolar elastase production, which may cause emphysema (54). Although research on MVs has not been as extensive as on OMVs, a previous study has revealed immunological responses to some common MVs in the airway. For example, Repeated airway exposure to *Staphylococcus aureus* EVs triggers both Th1 and Th17 responses, increasing neutrophilic inflammation through TLR2 (58). These results suggest that the pathogenicity of MEVs is strongly related to lung diseases. Understanding these immunological pathways is crucial for advancing pulmonary health research.

As aforementioned, numerous immune responses are triggered by MEVs, and it is evident that the mechanisms of these responses in the airways vary according to the Gram type of the bacteria. For example, common airway OMVs, such as those derived from *P. aeruginosa*, *E. coli* and *Acinetobacter baumannii*, increase IL-6 levels and neutrophilic activity (37,56,59). Meanwhile, MVs, such as those derived from S. aureus and *Faecalibacterium prausnitzii*, have been reported to commonly increase IFN-γ levels (58,60).

4. Clinical implications of the microbiome for lung cancer

Recently, interest in the relationship between the microbiome and human health and efforts toward clinical application have increased. Previous studies have suggested that the microbiome holds valuable information, demonstrating its potential as a material or biomarker for diagnosis, therapeutics and healthcare (Fig. 3) (24,61,62). After MEVs circulate throughout the body, they are excreted via feces, urine and exhaled air in their intact forms, unlike live microbes, which are restricted to the mucosal lumen or skin surface (43). Certain MEVs act as etiological agents of various diseases, while some MEVs have a protective role in disease pathogenesis. Therefore, circulating MEVs in our body provides us with noteworthy information for health and disease status (24).

Diagnostic potential of microbiome. Risk assessment, early diagnosis, treatment response prediction and disease monitoring are crucial for reducing mortality and enhancing quality of life in patients with cancer (63,64). There is a growing trend in developing diagnostic or screening technologies that utilize the microbiome-based quantitative polymerase chain reaction (qPCR), NGS, machine learning and enzyme-linked immunosorbent assay (Fig. 3). Most studies utilize fecal samples, which contain sufficient microbiomes for analysis, and therefore, research on microbiome-based diagnostics primarily targets gastrointestinal diseases. Previous studies on colorectal cancer diagnosis showed that a metagenomics algorithm achieved an area under the curve (AUC) of 0.89 (65), while qPCR demonstrated higher accuracy with an AUC of 0.93 (66). Additionally, this approach has been applied to lung cancer diagnostics using feces samples, with models using *Enterococcus*, *Streptococcus* and *Klebsiella* achieving an AUC of 0.96, a *Haemophilus*-specific model showing an AUC of 0.75 (20), and a model based on 13 OTU biomarkers demonstrating an AUC of 0.976 (22).

Recent studies have been conducted using diverse human samples, including urine, blood, saliva, bronchoalveolar lavage fluid (BALF) and sputum, with a focus on specific diseases, to development of diagnostic or screening technology based on microbiomes. For instance, to distinguish between benign lung disease and lung cancer using BALF, Kim *et al* (67) developed a prediction model based on *unclassified_SAR202_clade* (phylum Chloroflexi), achieving an AUC of 0.98, while a model using *Veillonella* and *Megasphaera* showed an AUC of 0.89 (23).

MEVs, rather than live microorganisms, are emerging as precise biomarkers for disease diagnostics using artificial intelligence (AI)-based analysis (61). McDowell *et al* (68) developed machine learning models using MEV metagenomes from serum, achieving AUCs of 0.93 for COPD, 0.99 for asthma and 0.94 for lung cancer. Antibodies against MEVs have also shown diagnostic potential, with IgG against MEVs derived from *S. aureus*, *Acinetobacter baumannii*, *Enterobacter cloacae* and *P. aeruginosa*, which are predominant in indoor dust, achieving AUCs of 0.78 for asthma, 0.79 for COPD and 0.81 for lung cancer (50).

MEV-based diagnostics have broad utility, with AUC of 0.95 for colorectal cancer using feces (69), 0.93 for brain tumor using blood (45), 0.87 for hepatocellular carcinoma using blood (70), 0.82 for gastric cancer using urine (71) and 1.00 for pancreatic cancer using blood (72). Furthermore, diagnostic models based on MEVs incorporating additional markers demonstrate improved performance. Combining MEV data with additional markers, such as metabolomics or tumor markers, significantly enhances diagnostic accuracy across various cancers (69,73). Thus, MEV-based diagnostic technologies, including composition assessment and immunoassays, can provide information on exposure to etiological agents (50). Additionally, MEVs derived from various samples can assist in the diagnosis of lung diseases.

5. Therapeutic potential of the microbiome

Live biotherapeutic products. Commensal bacteria are essential to human health, with growing recognition that humans are holobionts or supra-organisms. This means that the combined metabolic capabilities of both eukaryotic and prokaryotic components surpass those of each component alone (24). The U.S. Food and Drug Administration (FDA) has announced a new category called live biotherapeutic products (LBPs). The FDA has identified LBPs as biological products containing live organisms such as bacteria, which are used for disease prevention, treatment or cures, but are not vaccines (74). LBPs are administered in sufficient quantities to provide health benefits to the host (24,75).

Several studies have demonstrated the efficacy of LBP monotherapy. For examples, *Lactococcus lactis* inhibited lung cell proliferation (76,77). Other studies have shown that β-glucan, derived from Saccharomyces cerevisiae, can modulate immune responses and inhibit cancer cell viability in the lung cancer microenvironment (78,79). Short-chain fatty acids such as butyrate, propionate and acetate, when delivered from the gut to the lung, induce apoptosis in lung cancer cells (80). Although the exact mechanisms of LBPs remain unclear, immune system regulation and pathogen attachment interference are possible explanations.

LBPs can also be applied with regular treatments, such as conventional chemotherapy and immunotherapy, and have enhanced tumor suppression. Kotzampassi *et al* (81) found that the intake of *Lactobacillus* and *Bifidobacterium* reduced postoperative complications. In addition, Wada *et al* (82), demonstrated that the intake of *Bifidobacterium breve* during the chemotherapy period reduced the incidence of fever and decreased the need for intravenous antibiotics, thereby facilitating more effective therapy. Furthermore, combining *Lactobacillus* with cisplatin has been shown to reduce tumor size and increase immune responses in lung cancer models (83).

Microbial extracellular vesicles-based therapy as new-generation therapeutics. Recently, there has been a growing demand for developing new therapeutic targets distinct from conventional ones, suggesting the use of MEVs to address unmet medical needs as next-generation therapeutics. While the potential of using mammalian EVs for therapeutic purposes has been widely discussed, MEVs have yet to receive much attention thus far (84). Nevertheless, several studies have reported the beneficial effects of MEVs as therapeutic agents. EV derived from *Lactobacillus paracasei* significantly affects colorectal homeostasis in inflammation-mediated pathogenesis by attenuating LPS-induced inflammation in the intestine by activating endoplasmic reticulum stress (85). EVs derived from *Lactococcus lactis* can modulate airway inflammation by promoting a shift in immune responses from Th2 to Th1 by stimulating dendritic cells to produce IL-12, which offers a possible advantage for managing allergic asthma (86). Conversely, *Micrococcus luteus*-derived EVs alleviate neutrophilic airway inflammation by reducing IL-1β and IL-17 levels in BALF and inhibiting group 3 innate lymphoid cells activation through upregulation of microRNA (miRNA) in airway epithelial cells, proposing them as a potential therapeutic for unresolved neutrophilic asthma (87). Additionally, *Lactobacillus plantarum*-derived EVs have been suggested to treat atopic dermatitis, decreasing skin inflammation and epidermal thickness (88). EVs derived from *Bifidobacterium longum* have been shown to reduce the occurrence of diarrhea, which can be a symptom of food allergy, by inducing mast cell apoptosis without affecting T cell-mediated immune responses (89). Therefore, therapeutic strategies can utilize beneficial MEVs as potential immunomodulators while suppressing harmful MEVs by inhibiting their production or function (90). In addition, postbiotics represent a new modality for next-generation therapy to complement current cancer treatment, including those for lung cancer, such as small molecules, proteins, monoclonal antibodies and cell-based therapeutics (24).

Therefore, LBPs and MEVs-derived treatments can be used independently or as adjuncts to chemotherapy or immunotherapy, potentially becoming a major component of lung cancer treatment in the near future.

6. Healthcare potential of the microbiome

It has been demonstrated that the human microbiome is strongly associated with health. Therefore, it can be utilized within healthcare systems for: i) Vaccines; ii) supplements such as probiotics and postbiotics; and iii) monitoring systems.

Vaccine. Cancer vaccines primarily target tumor-specific antigens but often lack sufficient efficacy. Researchers are exploring the potential of combining probiotics with cancer vaccines to enhance their effectiveness. *Plasmodium*, the malaria parasite, shows promise as an adjuvant for cancer vaccines, particularly in combination with DNA vaccines (91). Additionally, MEVs can deliver genetic materials of vaccine components into target cells, potentially improving vaccine efficacy (92,93). MEVs, with their bilayered lipids, primarily containing LPS and outer membrane lipids, could also potentially be used to deliver beneficial proteins, miRNAs and act as adjuvants in vaccine development (62,94). Due to the variety of glycolipids and glycoproteins in their composition, MEVs can introduce biological activity into cells, making them suitable as drug delivery vehicles for cyclic nucleotides, enzymes and antitumor drugs (95-97). Recently, nano and micro materials, such as virus-like particles and liposomal vesicles, are also being explored for vaccine delivery (98,99). Kim *et al* (100) demonstrated the successful modification of OMVs as multifunctional vaccine delivery vehicles to enhance immune responses against cancer cells. This approach aims to boost the immune response against cancer cells. Ongoing research is investigating these combinations' potential to improve cancer treatment outcomes.

Supplements such as probiotics and postbiotics. Probiotics, or LBPs, are live microorganisms that, when consumed in adequate amounts, provide beneficial effects to the host and are widely used in clinical practice. Numerous studies suggest that microbiome intake plays a role in cancer prevention (77,101-112), initially evidenced by Goldin and Gorbach (100) in 1980, which showed that *Lactobacillus acidophilus* supplementation reduced intestinal cancer incidence in rat models. Subsequent studies, particularly *in vitro* research, have demonstrated that probiotics can reduce cell proliferation, induce cell cycle arrest and trigger apoptosis (102-106). Strains such as *Lactobacillus plantarum*, *Lactobacillus rhamnosus* and *Bifidobacterium polyfermenticus* have been shown to reduce tumor incidence and progression in animal models (107-111). However, most research focuses on gastrointestinal cancers, with limited studies on lung cancer. Preclinical data on mice suggest that *Lactococcus lactis* can inhibit cancer cell proliferation and proinflammatory cytokine production, showing promise for lung cancer prevention (77,112). Despite limited research on the use of probiotics for lung cancer, the findings mentioned are promising, and future studies are expected to yield further positive outcomes.

Postbiotics, including MEVs, are soluble factors released by microbes or after microbial lysis that provide physiological benefits (113). MEVs are emerging as key postbiotics in precision medicine, facilitating intercellular communication through proteins and small molecules enclosed in a lipid bilayer (114). Cell-to-cell communication is tightly regulated, and its disruption prompts disease advancement. Soluble factors include proteins and small molecules, and cell-to-cell communication is performed by MEVs, which are packages of information from microbial cells enclosed by a cell membrane. Moreover, recent scientific evidence has shown that certain MEVs as postbiotics have protective effects against disease development or progression (62,85,115,116).

Therefore, we propose that the intake of probiotics and postbiotics holds significant potential in the prevention of lung cancer, offering a hopeful avenue for future research and preventive measures.

Monitoring system. A healthcare monitoring system can be employed to track human health biomarkers by analyzing the airborne microbiome (34). Considering the significant association between human health and air pollution, which includes particulate matter, bioaerosols and gaseous substances, the vigilant monitoring of atmospheric pollutants can contribute to disease prevention. In numerous countries, bioaerosol regulation has been implemented through measurements based on culturing techniques (117). Culture-based analysis can directly observe bacteria in the air and yield colony-forming units. However, this method faces several limitations: i) It can only measure bacteria counted >1% of the total in a solid medium agar plate (118); ii) it is restricted to analyzing specific bacterial species; and iii) it is incapable of analyzing unculturable bacterial material such as MEVs and dead bacteria. For these reasons, numerous studies are underway to enable real-time on-site monitoring of bioaerosols and biomarkers related to human health. Cho *et al* (119) developed the bioaerosol monitoring system based on ATP extracted from *E. coli* and demonstrated that this system can continuously monitor with high sensitivity in real-time. Additionally, a previous study has utilized reverse transcription-PCR to detect airborne bacteria (120). Furthermore, to facilitate the precise and rapid detection of bioaerosols, droplet digital PCR (ddPCR) has been employed extensively in various studies for pathogen diagnosis, mutation detection and transgenic research (120-122). For instance, airborne *Mycobacterium tuberculosis* was detected using ddPCR (123); however, this method currently cannot detect airborne bacteria in real-time on-site, indicating that the technology requires further improvement.

Through such monitoring systems, lung cancer surveillance can be enhanced. Furthermore, by observing microbiomes associated with lung cancer risk, these systems have the potential to utilize these microbiomes as biomarkers for the disease.

7. Conclusion

The present review explored the potential of microbiomes and MEVs as innovative tools in precision medicine for lung cancer. Disease patterns are linked to cellular aging and elevated reactive oxygen species, contributing to conditions such as inflammation, immune diseases and cancer. There is a growing shift toward promoting health through advanced diagnostics, safer therapeutics and prevention-focused healthcare systems. To support this shift, advancements in biological data analysis, including metagenomics and AI technologies such as machine learning, are essential for disease prediction and personalized therapies. While significant research on the microbiome exists, understanding the interactions between microbiota and host, particularly microbial products, remains limited. A deeper understanding of these interactions is key to developing beneficial microbial products. MEVs, unlike LBPs, can penetrate cells and target distant organs, offering significant advantages as diagnostic biomarkers and therapeutic candidates. We propose MEVs as next-generation technologies

for lung cancer, capable of replacing current biologics such as proteins, antibodies and genes.

Future research on MEVs is expected to enhance our understanding of their role in lung cancer and foster precision medicine approaches, including diagnostics and therapies utilizing MEVs from beneficial microorganisms.

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Availability of data and materials

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Authors' contributions

JYJ and JHS conducted the literature research, developed the methodology, generated the figures, and wrote the original draft. HJR, JJC, HY, and DMH contributed to the literature research and edited the manuscript. JY conceptualized the study, acquired funding, conducted the investigation, managed the project, supervised the research, visualized the results, and reviewed and edited the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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