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UNLOCKING THE SECRETS OF GUT-LUNG MICROBIOME

Medical Science

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ABSTRACT

A common saying states, “You are what you eat.” Indeed, nutrition and diet play an important role in regulating the number of different microorganisms that live in the gut. This means that diet may also play a key role in the immune function. Microbial components include pathogen-associated molecular patterns (PAMPs), such as peptidoglycans and lipopolysaccharides. Short-chain fatty acids (SCFAs) produced from the fermentation of dietary fiber by gut bacteria, SCFAs as acetate, propionate, and butyrate, are crucial for gut health and can also influence energy metabolism and brain function. Trimethylamine N-oxide (TMAO), formed from dietary choline and carnitine, TMAO is linked to cardiovascular diseases and may also affect brain function. One of the metabolites of gut microbiota has been proven to aggravate pulmonary hypertension. Overall purine metabolism and in key enzymes that metabolize purines and produce urates, such as xanthine oxidase and purine nucleosidase, in the gut microbiota of Pulmonary hypertension patients. Tryptophan and Indole-derivative metabolites are produced from dietary tryptophan and play a role in regulating immune function and may influence neurological disorders. Bile acids and salts which are involved in fat digestion and absorption, and these modified bile acids can also act as signals for other organs. Smoking is the predominant risk factor for COPD, but only some smokers develop COPD. Why this happens is unknown, but new techniques in the culture of microorganisms have shed some light on the possible link between the gut and lung microbiomes and COPD pathogenesis.

KEYWORDS

Gut microbiota, Gut–lung axis, Pulmonary hypertension, COPD,Lung cancer, pathogen-associated molecular patterns (PAMPs), Trimethylamine N-oxide (TMAO), Short-chain fatty acids (SCFAs)

INTRODUCTION

There is a clear crosstalk between the two sites known as the gut-lung axis, which was reported recently (1)

In general, lung cancer can be classified into two major types in accordance with their histological presentations, including small cell lung cancer(SCLC) and non-small cell lung cancer (NSCLC), which the latter one could be further divided into four subtypes based on their cellular and molecular variations: Lung adenocarcinoma (LUAD), Lung squamous cell carcinoma (LUSC), Bronchial carcinoid tumor, as well as Large cell carcinoma (2).

Available evidence revealed that alterations of specific gut flora could contribute to the lung cell mutagenesis through changing metabolism, creating an immunosuppressive microenvironment, as well as activating inflammatory pathways (3,4)

Apart from the gut epithelium, microbes are also identified to colonize epithelial surfaces of the respiratory tract, participating in maintaining barrier integration and immune homeostasis of the respiratory epithelium, but can also drive lung cancer progression (5)

Dysbiosis of the gut microbiota may play a pathophysiological role in lung disease by altering immune, hormonal, and metabolic homeostasis (6,7)

Interestingly, gut and lung microorganisms are interlinked by a bidirectional axis via lymphatic and blood circulation; hence, modification of one compartment will, in turn, impact distant epithelial bioactivities, which brings forth the coining of the concept of “gut-lung axis” (8)

However, emerging evidence reveals a complex, bidirectional communication network between these systems, referred to as the gut–lung axis, which may significantly impact the function and health of both the gut and the respiratory system (9)

Furthermore, preclinical and clinical studies have pointed out that gut microbes could modify the anticancer response of various lung cancer treatments, including chemotherapy, radiotherapy, targeted therapy, and in particular, immunotherapy (10)

Beyond these metabolic roles, the gut microbiota is integral to immune function, promoting the growth and maturation of immune cells through microbial sensing and providing local and systemic signals that help shape immune responses (11)

The gut microbiota refers to the diverse microorganisms that widely distribute and inhabit the GI tract, participating in maintaining the intestinal tract's physiological and immunological stabilities (12)

The integrity of gut microbes is considered indispensable for the overall health of the host. (13)

Certain microbiota pathogens in the lungs and intestines have been discovered to be capable of affecting the occurrence, development, and prognosis of diseases through different means, such as inflammation, metabolism, and cell signalling (14,15).

Clinically, lung diseases, such as asthma, chronic obstructive pulmonary disease (COPD), and even lung cancer, are often associated with digestive tract diseases, resulting in prolonged disease courses, aggravated diseases, and increased mortality (16)

Changes in microbial composition and function, termed dysbiosis, in the respiratory tract and the gut have recently been linked to alterations in immune responses and to disease development in the lungs (17)

According to Zhang et al., Bacteroidetes, *Cyanobacteria*, Fusobacteria, *Lentisphaerae*, and Spirochaetes were detected to be more abundant in lung cancer patients, while another two strains (Firmicutes and Verrucomicrobia) were dramatically diminished compared to healthy groups ($p < 0.05$) (18)

Actinobacteria, Firmicutes, and Bacteroidetes predominate in the gut, and Proteobacteria, Firmicutes, and Bacteroidetes dominate in the lungs (19)

The gut and lung microbiota show a close relationship throughout life, indicating a host-wide network between them (20)

History Of The Lung Microbiome

The study of the lung microbiome is still in its infancy compared to that of the microbiomes of other parts of the body. (21)

However, most of the subsequent studies focused on the functions of the gut microbiome, fecal microbiome, etc., in the lung(22)

It was evident that the lungs were in a sterile state, which was most people at that time. In 2010, researchers successively determined the composition of the airway microbiota; thus, the microbiome in the respiratory system came to light (23)

With further advances in detection technology, scientists have applied computed tomography (CT) scans, PCR, and 16S rRNA sequencing to investigate the lung microbiome (24)

At the same time, Foder et al. found that adult CF is closely related to the microbiome (25)

Not only are the survival and prognosis of patients with COPD related to lung microorganisms, but pneumonia and bronchial diseases also involve an imbalance in pulmonary microorganisms. (26,27)

In 2014, researchers focused on the relationship between lung transplantation and the microbiome, showing that the impact of the lung microbiome on innate and adaptive immune responses is beginning to be explored (28,29)

With the further elaboration of the concept of the "microbiome", the focus is no longer limited to bacterial communities but also fungal and viral communities.(30)

Immunity

Lung diseases are usually accompanied by dysbiosis of the intestinal flora and an immune-inflammatory response.

Gut microbiota influences both the gut immune system and the lung immune system via local or long-reaching interactions, which involve either CD8+ T cell, T helper (Th17) cells, interleukin 25 (IL-25), interleukin-13 (IL-13), prostaglandin E2, and nuclear factor-kappa B (NF-κB)–dependent pathways. (31,32)

Any problems in the gut barrier may cause microbial translocation into the bloodstream and make a sustained inflammatory response, which leads to lung injury, pulmonary fibrosis, and carcinogenesis (33,34)

Changes in the number or function of gut microbiota can also affect health. Possible mechanisms include regulation of the extraintestinal T-cell population, development of oral immune tolerance through regulatory T cells (Tregs), production of short-chain fatty acids (SCFAs), and regulation of systemic inflammation. (35,36)

The lung microbiota impacts mucosal immunity and contributes to immune tolerance through neutrophil recruitment, production of pro-inflammatory cytokines mediated by receptor 2 (TLR2), and the release of antimicrobial peptides, such as β-defensin 2, stimulated by Th17 cells. (37,38)

The gut mucosa is exposed to a large variety of external antigens. T helper (Th) cells come into play when antigen-presenting cells (APCs) identify microorganism antigens, leading to cytokine production and, eventually, the activation and differentiation of Th cells. (39)

In the gut, the harmonic balance of Th/Treg cells is usually attained by in situ induction of these cells from naïve T cells, recruitment of differentiated Th/Treg cells into the tissue, and reprogramming of already differentiated Th/Treg cells towards other lineages in peripheral tissues (40)

$CD4^+$ T cells are split into two subclasses: Th and Treg cells. Th cells are an essential part of the adaptive immune system in synchronizing the defense against pathogens. They play an important role through their distinctive cytokines and effector functions in guiding tissue inflammation. Within the Th subsets, Th1 cells produce interferon-gamma (IFN-γ) as protection against intracellular pathogens, Th2 cells produce interleukin 4 (IL-4), IL-5, and IL-13 to clear parasitic pathogens, and Th17 cells produce IL-17, IL-21, and IL-22 to control microbial pathogens (41)

The concept of suppressor T cells can downregulate the activity of other T cells. (42)

Both Th17 and Tregs have shown commonality despite their functional dissimilarities and are highly represented in the periphery of the intestine. They comprise miscellaneous subpopulations with the ability to alter suppressor or effector capabilities in different circumstances (44)

"The Battle of the Gut Microbiota,

Microbial ecology, the study of the interactions between microorganisms and their environment, plays a crucial role in understanding the structure and function of microbial communities in the human gut and respiratory tract.

Microbiomes in the human gut not only help in the digestion of food but also control functions of other organs like the liver, according to a new study. Bifidobacteria, in the intestine, digest the healthy sugars in breast milk that are important for growth. Other bacteria digest fiber, producing short-chain fatty acids, which are important for gut health. The gut microbiome controls the immune system and infection. Recent research suggests that the gut microbiome affects the central nervous system and controls brain function. Gut bacteria produce certain vitamins, including vitamin K. Bifidobacteria and Lactobacilli, found in probiotics and yogurt, can help seal gaps between intestinal cells and prevent leaky gut syndrome. Flavonoids are the antioxidants found in plants.

Chronic respiratory diseases, including asthma and chronic obstructive pulmonary disease (COPD), as well as respiratory virus infection, are often accompanied by gastrointestinal diseases or symptoms. (45,46)

Patients with gastrointestinal diseases, such as inflammatory bowel disease (IBD) and gastroesophageal reflux, are prone to develop pulmonary dysfunction and have an increased incidence of respiratory disease. These connections suggest a vital communication between the gut and lungs.(47,48)

The significance of gut microbiota

Human health is an ever-interesting topic. Several studies have been carried out on the same, exploring the various genera involved, the association between them, and their importance in maintaining good health. The healthy human gut is colonised mainly by organisms belonging to two phyla, namely Bacteroidetes and Firmicutes. They have been found to play inevitable roles in host nutrient metabolism, maintaining the integrity of gut mucosa, and protection from invading pathogens.

Mice have always been excellent models for pharmaceutical research. They have also been proven useful in studying the interaction between the host and intestinal microbes. Since human beings and mice occupy a common niche, there might be a significant association between their gut microbiota. According to earlier studies, mice gut microbiota shows considerable similarity to the human gut microbiome.(49)

The Microbiome Gives And Takes Between The Gut And Lungs

Emerging findings indicate there is a vital cross-talk between gut microbiota and the lungs, which is known as the Gut and Lung Axis.

Actinobacteria, Firmicutes, and Bacteroidetes predominate in the gut, and Proteobacteria, Firmicutes, and Bacteroidetes dominate in the lungs (50)

The gut and lung microbiota show a close relationship throughout life, indicating a host-wide network between them (51)

It was also reported that gut and lung abundances are highly correlated over time.

Changes in diet alter gut colonisation patterns and colonization with

Roseburia, Dorea, Coprococcus, Blautia, or *Escherichia* presage their appearance in the respiratory tract. The literature on the direct transfer of microorganisms between the gut and lungs is very limited. Various hypotheses have been postulated to explain gut-lung translocation, such as the gut-lymph theory (52,53)

Scientific evidence shows that the barrier integrity is compromised in cystic fibrosis, sepsis, and acute respiratory distress syndrome, suggesting gut-lung translocation of microorganisms demonstrated that the lung microbiota is enriched with gut bacteria, such as *Bacteroides* spp., after sepsis and acute respiratory distress syndrome. (54)

Gut Microbial-Derived Metabolites -

Gut bacteria produce small molecules of metabolites. These metabolites act as communication signals between the gut and other parts of the body, like the lungs and the brain.

The important metabolites are

Short-chain fatty acids (SCFAs):

Produced from the fermentation of dietary fiber by gut bacteria, SCFAs like acetate, propionate, and butyrate are crucial for gut health and can also influence energy metabolism and brain function.

Trimethylamine N-oxide (TMAO):

Formed from dietary choline and carnitine, TMAO is linked to cardiovascular diseases and may also affect brain function. One of the metabolites of gut microbiota has been proven to aggravate pulmonary hypertension.

Overall purine metabolism and in key enzymes that metabolize purines and produce urates, such as xanthine oxidase and purine nucleosidase, in the gut microbiota of Pulmonary hypertension patients.

Tryptophan And Indole-derivative Metabolites:

These metabolites are produced from dietary tryptophan and play a role in regulating immune function and may influence neurological disorders.

Bile Acids And Salts:

The gut microbiota can modify bile acids, which are involved in fat digestion and absorption, and these modified bile acids can also act as signals for other organs.

The Involvement Of Metabolites.

1. SCFAs enhance glucose uptake and lipid oxidation, reducing the risk of metabolic disorders.
2. Gut metabolites can modulate the immune response.
3. These metabolites can influence the gut-brain axis, potentially impacting brain function and mood.
4. The metabolites, like bile acids, SCFAs, and tryptophan metabolites, are associated with the disease.
5. Gut metabolites, particularly SCFAs and TMAO, are being investigated for their potential role in the development and progression of Alzheimer's disease (AD).

Lung diseases associated with gut microbiota

Pulmonary hypertension (PH)

Pulmonary hypertension (PH) is a severe, progressive, and fatal cardiopulmonary disease characterized by inflammation, pulmonary vascular remodeling, and vascular occlusion leading to increased pulmonary artery pressure and pulmonary vascular resistance, right ventricular insufficiency, left ventricular compression, and heart failure (55,56)

Some evidence supported the hypothesis of dysfunction of the gut-lung axis in PH. 16S rRNA sequencing results showed that in the flora composition of rats with PH, there was an increase in Clostridiales, Aerococcaceae, *Oscillospira,* and Roseburia et al., and a decrease in Bifidobacteria, Streptococcus, Akkermansia, *Marvinbryantia, and Dehalobacterium* et al. Among them, some beneficial flora can induce Tregs and inhibit the expression of inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-1β (IL-1β) to inhibit vascular inflammation(57,58)

Trimethylamine N-oxide (TMAO), one of the metabolites of gut microbiota, has been proven to aggravate pulmonary hypertension. Mice fed a high-fat, high-choline diet for 8 weeks had pulmonary hypertension associated with pulmonary vascular remodelling compared with mice fed a conventional diet. As choline is a precursor to TMAO, the gut microbiome likely influenced the development of pulmonary artery remodeling and pulmonary hypertension in this model (59)

In human samples, it is found that there is a significant increase in overall purine metabolism and in key enzymes that metabolize purines and produce urates, such as xanthine oxidase and purine nucleosidase, in the gut microbiota of PH patients. This result suggests that it is necessary to make a further study about the mechanisms of gut microbial-derived purines and urates in PH (60)

Chronic Obstructive Pulmonary Disease (COPD)

Smoking is the predominant risk factor for COPD, but only some smokers develop COPD. Why this happens is unknown, but new techniques in the culture of microorganisms have shed some light on the possible link between the gut and lung microbiomes and COPD pathogenesis. Because of the gut–lung axis hypothesis, interest in whether lung and gut microbiomes relate to the pathogenesis of COPD has increased. The relationship between the lung microbiome reflected by either sputum, bronchoalveolar lavage fluid (BALF), or lung tissue and the gut microbiome reflected by fecal samples and the pathogenesis of COPD has been recently presented (61)

A theory known as the vicious circle hypothesis describes the pathogenesis of COPD. It states lung dysbiosis provides a constant inflammatory stimulus in COPD (62).

Lung Cancer

Gut-organ crosstalk has been confirmed in other cancer-related studies; however, whether there is a similar relationship in lung cancer is less known. In recent decades, immunotherapy has become the focus of lung cancer research (63)

Since the discovery of immune checkpoint proteins, there has been a special interest in developing antibodies that block programmed cell death 1 receptor (PD-1) and programmed cell death receptor ligand 1 (PD-L1) for a subset of cancer patients. PD-1 signalling negatively regulates T cell-mediated immune responses and serves as a mechanism for tumours to evade an antigen-specific T cell immunologic response. It plays a role in promoting cancer development and progression by enhancing tumour cell survival. With this background, PD-1 signalling represents a valuable therapeutic target for novel and effective cancer immunotherapy. Clinical data show that blockade of this PD-1 signalling significantly enhances antitumor immunity, produces durable clinical responses, and prolongs survival. Currently, there are three FDA-approved PD-L1 inhibitors for various malignancies, ranging from non-small cell lung cancer to Merkel cell carcinoma. (64)

Gut dysbiosis is involved in carcinogenesis and the progression of lung cancer through genotoxicity, systemic inflammation, and defective immunosurveillance. In addition, the gut microbiome harbours the potential to be a novel biomarker for predicting sensitivity and adverse reactions to immunotherapy in patients with lung cancer. Probiotics and fecal microbiota transplantation (FMT) can enhance the efficacy and depress the toxicity of immune checkpoint inhibitors by regulating the gut microbiota. (65)

CONCLUSION

Human gut microbiomes exhibit individual precision. The human gut possesses millions of microbes that define a complex microbial community. The gut microbiota has been characterized as a vital organ forming its multidirectional connecting axis with other organs. This gut microbiota axis is responsible for host-microbe interactions and works by communicating with the neural, endocrinal, humoral, immunological, and metabolic pathways. The gut microbiota communicates with the lungs via soluble microbial components and bacterial metabolites, which reach the systemic circulation. The attention has been shifted from prospective studies to clinical trials to have a better understanding of how microbiota can interplay in human health and disease.

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