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Influence of Gut and Lung Microbiota and the Gut-Lung Axis on Bronchopulmonary Dysplasia

Binxiang Xu, Yumei Liang*

Affiliated Hospital of Youjiang Medical University for Nationalities, Baise 533000, Guangxi Province, China

***Corresponding author:** Yumei Liang, LYM8591@163.com

Abstract: Bronchopulmonary dysplasia (BPD), also known as neonatal chronic lung disease, is a common respiratory disease in preterm infants. Preterm infants with BPD often exhibit changes in gut and lung microbiota. In recent years, with the development of high-throughput sequencing technology, more and more mechanisms of the gut-lung axis have been confirmed, helping to explore new directions for the treatment of BPD using microecological agents. This paper reviews the roles of gut microbiota, lung microbiota, and the gut-lung axis in the pathogenesis of BPD in preterm infants, providing new research avenues for the prevention and treatment of BPD.

Keywords: Bronchopulmonary dysplasia; Gut-lung axis; Gut microbiota; Lung microbiota

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1. Introduction

Current research largely agrees that the risk factors for bronchopulmonary dysplasia (BPD) include prematurity, mechanical ventilation, oxygen toxicity, infection, and genetic factors. The lung injury caused by BPD is believed to result from inflammation, oxidative stress, and abnormal growth factor signaling [1]. Recent in-depth studies of the gut-lung axis have revealed that gut microbiota can influence the progression of BPD through various pathways, including disruption of the gut barrier, metabolites, and immune regulation. Therefore, studying the mechanisms through which lung and gut microbiota affect BPD is of great importance for preventing, treating, and improving the prognosis of the disease. This paper provides an overview of the latest research on the roles of gut microbiota, lung microbiota, and the gut-lung axis in the progression of BPD.

2. The establishment of gut microbiota in preterm infants and its correlation with BPD

The vast collective of bacteria living in the human gut is called gut microbiota, with a total number of bacteria

reaching 10^{14}, which is nearly 10 times the number of human cells. The number of genes encoded by these bacteria is 100 times that of the human genome, which is why gut microbiota is also referred to as the human "second genome." Previous sterile placenta view was considered sterile *in utero* [2], but the new research has shown that during pregnancy, the mother's microbiota and its metabolites begin to transfer to the fetus through the maternal gut-placenta axis, affecting the development of the fetal immune system [3]. Since preterm infants have underdeveloped immune and digestive systems, the formation of the neonatal gut microbiota is influenced by various prenatal and postnatal factors, such as gestational age, mode of delivery, feeding method, and antibiotic use [4,5]. The diversity and abundance of specific bacterial species in the gut microbiota of preterm infants are lower than those of full-term infants [6]. The primary bacteria in the gut microbiota of preterm infants include *Enterococcus*, *Veillonella*, *Bifidobacterium*, and *Enterobacteriaceae* [7,8], which play important roles in the growth and development of preterm infants.

In recent years, numerous studies have been conducted both domestically and internationally on the gut microbiota of preterm infants with BPD, revealing varying degrees of dysbiosis, which may be related to the occurrence and progression of BPD. Ryan *et al.* [9] conducted transcriptome sequencing analysis on 250 stool samples from infants with BPD and found that three genera (*Escherichia*/*Shigella*, *Klebsiella*, and *Salmonella*) were significantly associated with the diagnosis of BPD. Chen *et al.* [10] conducted a case-control study to investigate the composition of gut microbiota in infants with BPD and found that the four dominant phyla in the gut microbiota of the BPD group were Actinobacteria, Proteobacteria, Bacteroidetes, and Fungi, which were relatively lower than the normal group. Another study found that disruption of gut microbiota by antibiotic exposure led to more severe BPD in mice [11].

3. Correlation between lung microbiota and BPD

Some researchers have discovered that the lungs are not sterile organs. Wang *et al.* [12] demonstrated through bacterial culture of amniotic fluid that bacteria in the amniotic fluid could colonize the fetal respiratory tract early on via the placenta or swallowing. At birth, the gut microbiota of newborns is relatively simple, but it becomes more diverse within a few months after birth, reaching stability at around 2–3 years of age. The development of lung microbiota is primarily influenced by factors such as gestational age, mode of delivery, feeding method, and antibiotic use. Gestational age significantly affects lung microbiota differences, with *Staphylococcus* and *Ureaplasma* being the dominant species in preterm infants' lungs, while *Streptococcus* and *Neisseria* are more common in full-term infants' lung microbiota [13].

Relevant studies have found that the respiratory microbiota of newborns delivered vaginally mainly originates from the mother's vaginal microbiota, such as *Lactobacillus* and *Corynebacterium*, whereas the respiratory microbiota of newborns born via cesarean section mainly comes from the skin, including *Streptococcus* and *Propionibacterium* [14]. Additionally, sputum cultures from neonates with lower respiratory tract infections indicate a higher positive rate of *Staphylococcus aureus* and *Streptococcus* in cesarean-delivered infants [15]. Feeding methods also affect neonatal lung microbiota. Breastfeeding helps maintain and promote healthy lung microbiota, while formula feeding may lead to microbiota imbalance, potentially related to tryptophan metabolism, which increases the risk of respiratory diseases [16].

Among these factors, the idea that antibiotics disrupt the homeostasis of respiratory microbiota is widely accepted. Preterm infants, due to their underdeveloped immune systems, higher hospitalization rates, and

increased infection risks, are more likely to receive antibiotics. Studies have found that the gut microbiota of preterm infants is dominated by facultative anaerobes, including *Enterobacteriaceae*, *Enterococcus*, and *Staphylococcus*, and these communities often contain antibiotic-resistant microbes [13].

As our understanding of lung microbial ecology deepens, it has become clear that lung microbiota interacts with local cells and the environment, ultimately influencing disease pathogenesis [17]. Currently, the characteristics of lung microbiota in the context of BPD have become a research focus. BPD has a high incidence in preterm infants, and the longer duration of mechanical ventilation in these infants increases the incidence of ventilator-associated pneumonia (VAP), which in turn leads to lung microbiota dysbiosis in infants with BPD [18]. Researchers have found an increased abundance of *Escherichia* and *Shigella* in the gut microbiota of preterm infants with BPD, while the abundance of *Klebsiella* and *Salmonella* decreased [9]. Additionally, the lung microbiota of infants with varying degrees of BPD severity differs. Studies have shown that in infants with severe BPD who receive prolonged ventilation, there is a significant increase in *Corynebacterium* in the airway microbiota [19]. Animal experiments have also confirmed that BPD affects gut microbiota. Li *et al.* [20] studied the lung microbiota of adolescent mice with a BPD model and found dysbiosis, with decreased *Corynebacterium* and increased *Staphylococcus* abundance in the lungs of the BPD model mice.

4. Mechanism of the gut-lung axis in BPD disease progression

Traditional Chinese medicine has long recognized a connection between the lungs and the gastrointestinal tract, proposing the theory that "the lungs and large intestine are interior-exteriorly related." Modern research in microbial ecology has similarly revealed physiological and pathological interactions between the lungs and intestines, coining the term "gut-lung axis" to describe this interplay. The mechanism of the gut-lung axis in BPD disease progression can be explained through three aspects: gut barrier disruption, metabolic dysregulation, and immune regulation.

4.1. Gut barrier disruption

The gut barrier mainly relies on the mucosal immune system, which is widely distributed across the gastrointestinal tract, respiratory tract, urogenital tract, and other mucosal tissues, serving as the primary site for local immune functions. The intestines are the body's largest immune organ, and activated T cells and B cells in the intestinal mucosal immune system can travel to other mucosa-associated lymphoid tissues (such as the respiratory tract and reproductive tract) and elicit immune responses to the same antigens. This phenomenon is known as the common mucosal immune system. When a person becomes ill, the gut barrier function is disrupted, increasing the permeability of the intestinal mucosa. This allows inflammatory mediators and gut bacteria to translocate to the lungs, causing inflammation and damage [21]. Research by Ma *et al.* [22] found that mesenteric lymph, due to its abundance of albumin, high-density lipoproteins, and protease inhibitors, exhibits anti-inflammatory and barrier-protective properties. In situations of local or systemic stress following gut injury, mesenteric lymph transports gut-derived cytotoxic/inflammatory mediators to the pulmonary circulation, contributing to inflammation and leading to acute lung injury.

4.2. Metabolic dysregulation

In recent years, with deeper research into the relationship between BPD and the metabolic products of gut

microbiota, more connections between BPD and gut microbiota metabolites have been uncovered. Fanos *et al.* [23] conducted research on neonatal urine metabolites and found that BPD infants had significantly elevated levels of metabolites such as inositol, lactate, taurine, and trimethylamine-N-oxide (TMAO), while gluconate levels were significantly reduced. The role of Toll-like receptors (TLRs) in recognizing lipopolysaccharides has been confirmed to play an important role in the link between gut microbiota and the lungs [24]. TLRs bind to lipopolysaccharides in microbial metabolites, elevating the level of interleukins in the body and activating nuclear factor κB, which leads to more severe pulmonary inflammatory damage [25]. Acetate, a metabolite produced by gut microbiota, has been found in animal studies to alleviate lung injury caused by hyperoxia exposure by inhibiting the expression of nlrp3-related proteins and affecting the abundance of gut microbiota. This suggests that abnormal acetate metabolism may be an important factor in the onset of BPD [26]. Gut microbiota can metabolize dietary fiber into short-chain fatty acids (SCFAs), gamma-aminobutyric acid (GABA), and histamine [27], among which SCFAs play a significant role in the development and progression of BPD.

4.3. Immune regulation

Before birth, the lung immune system is primarily composed of Th2 cells. After birth, the polarization of immature T cells in the lungs shifts from a Th2 to a Th1 phenotype. After being taken up by dendritic cells (DCs), gut microbiota alters the phenotype of DCs, which then migrate from the intestines to mesenteric lymph nodes. Through antigen presentation, DCs induce the activation of T cells, thereby triggering immune responses in the lungs [28]. Moreover, innate lymphoid cells (ILCs) also play a crucial role in immune regulation within the gut-lung axis. ILCs in the intestines enter the bloodstream via the lymphatic circulation and subsequently reach the lungs, where they participate in the repair of pulmonary inflammatory damage [29]. Australian researchers have also discovered significant changes in the expression of red blood cells and immune-related genes in BPD infants, suggesting that immune-related genes also play a regulatory role in BPD [9].

5. Summary and outlook

BPD is a common respiratory disease in preterm infants with complex pathogenesis and many influencing factors. Current research on the gut-lung axis mainly focuses on the role of the intestinal mucosal barrier, microbiota metabolism, and immune regulation. However, research is still in its early stages, and more characteristics of the gut and lung microbiota and the mechanisms of the gut-lung axis remain to be discovered. The safety and efficacy of fecal microbiota transplantation need further validation. In-depth research into the influence of gut and lung microbiota, as well as the gut-lung axis on bronchopulmonary dysplasia, may provide new insights and treatment strategies for the clinical management of BPD in preterm infants.

Disclosure statement

The authors declare no conflict of interest.

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