The Clinical Progress of the Combined Treatment of Lung and Intestine on Immune Response

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Abstract: Lung-intestinal homoeopathy is a comprehensive therapeutic strategy that combines traditional theories of traditional Chinese medicine and modern medical concepts. We review the clinical progress of lung-gut homoeopathy on immune function. aiming to positively affect the immune function of patients with lung diseases. By regulating the intestinal microbiota, influencing intestinal mucosal immunity, and modulating immune mediators, some clinical treatments has been proved to be effective. In addition, lung-intestinal homoeopathy can improve the immune function of patients with lung diseases by regulating the expression of immunity and immune mediators in the intestinal mucosa and influencing the play of immune response. Although lung-intestinal homoeopathy has made some progress in the regulation of immune function, further clinical studies are needed to verify its efficacy and safety.
***Keywords*:** lung-gut axis, immunity, clinical, Chinese medicine

1. Introduction

Clinical observations have revealed that patients with pulmonary diseases often exhibit gastrointestinal dysfunction. The gastrointestinal tract the largest immune organ and a crucial defense line of the host immune system. Experimental evidence has demonstrated an association between gastrointestinal dysfunction and impaired intestinal barrier function, leading to dysregulation of the host immune response. The respiratory and digestive tracts share a common origin from the endoderm, allowing lymphocytes to migrate between the respiratory and digestive tracts through peripheral circulation[1]. Khailova demonstrated in a pneumonia animal model infected with Pseudomonas aeruginosa that intestinal mucosal epithelial apoptosis increased, accompanied by a significant upregulation of pro-inflammatory cytokine mRNA expression[2]. With the assistance of Th1 and Th2 CD4+ T lymphocytes, B cells derived from gut-associated lymphoid tissue (GALT) can induce the secretion of secretory IgA (S-IgA). Commensal bacteria residing in GALT can also induce plasma cells to produce abundant S-IgA to protect the intestinal barrier[3]. The integrity of intestinal epithelial cells and structures ensures robust mucosal immunity. Inflammatory factors, microorganisms, their metabolites, and exogenous substances in the gastrointestinal tract can influence the lungs through local and systemic immune responses. These findings underscore the importance of intact lung and intestinal epithelium as prerequisites for normal mucosal immune function, with mutual immune migration between the two influencing each other.

2. Clinical Advances

2.1 Chronic airway inflammatory diseases

Dysbiosis in the gut microbiota can affect the lungs via lymphatic and bloodstream circulation, contributing to extrapulmonary organ diseases[4]. Treatments utilizing the lung-gut axis approach have shown promising results in patients with acute exacerbation of COPD undergoing mechanical ventilation. A therapy regimen significantly improved gastrointestinal symptoms, oxygenation, and mechanical ventilation duration compared to conventional treatment, with reduced complications and superior efficacy over pure Western medicine intervention[5]. In COPD mouse models, inflammatory ILC2s (iILC2) and natural ILC2s (nILC2) are notably increased in both intestinal and lung tissues. The underlying mechanism may involve the activation of ILC2 subsets, promoting Th2 cell secretion of IL-13 and IL-4, migration to pulmonary tissues via lymphatic and bloodstream circulation, recruitment of monocytes and lymphocytes[6].In a cigarette smoke-induced COPD mouse model, enlarged gut-associated lymphoid tissue in the distal small intestine stimulates the intestinal immune system, altering the differentiation process of B cells, as well as the interaction among B cells, T cells, and dendritic cells, with increased IgA expression[7].

2.2 Infectious diseases of the lungs

Pulmonary infections often present with gastrointestinal symptoms, such as abdominal pain, diarrhea, constipation, and gastrointestinal bleeding. Pathogens, whether bacterial, viral, fungal, or mycobacterial, disrupt the intestinal microbiota upon invasion, leading to dysregulation of host intestinal immune function. Research in a COVID-19 rhesus macaque model demonstrates that nasal viral infection activates macrophages in the digestive system, leading to the secretion of inflammatory cytokines and gastrointestinal tissue damage[8]. Xuan Bai Cheng Qi decoction acts on the Foxp3/RORyt signaling pathway, modulating Treg and Th17 cell-mediated pulmonary-intestinal immune imbalance[9]. Fecal microbiota transplantation (FMT) in Pseudomonas aeruginosa-infected mice restores intestinal microbial abundance and diversity, suppresses inflammation and tissue damage, and improves Treg/Th17 cell immune balance[10]. Following antibiotic treatment during pregnancy, neonatal mice inoculated with bacillus Calmette-Guérin did not show alterations in the number of TB10.4 T cell epitopes, suggesting that maternal antibiotic use during pregnancy may contribute to the development of immune defects and alter offspring susceptibility to Mycobacterium tuberculosis[11].

2.3 Interstitial lung diseases

The potential mechanism involves dysbiosis of lung and intestinal microbiota post-IPF, stimulating the release of inflammatory factors, leading to immune dysregulation both locally and systemically. Additionally, pathological alveolar macrophages are an important source of chemokines and cytokines during IPF□contributing to pulmonary fibrosis are predominantly derived from circulating monocytes[12]. Recent studies have highlighted the significance of traditional Chinese medicine polysaccharides effectively ameliorate abnormal recruitment and apoptosis of various cells induced by the TGF-β signaling pathway in lung tissues, regulate systemic imbalance caused by pulmonary inflammation, and suppress lung tissue damage through oxidative stress modulation, thereby inhibiting the progression of pulmonary fibrosis[13]. Studies have previously shown that a causal association exists between microbiota and pulmonary cellular immune responses in lung injury and fibrosis. Others noted key changes in the adaptive immune response with increased numbers of CD4+ □IL-10 lymphocytes and Th1 lymphocytes in FMT recipient mice compared with GF mice. We concluded that horizontal transmission of microbiota by cohousing attenuated mortality in mice and promoted a transcriptionally altered pulmonary immunity[14]. MXHQD could significantly inhibit the elevation of ZBP1 and ISG15 factors induced by the fibrosis model, which related to immune system and anti-virus[15].

2.4 Acute Lung Injury/Acute Respiratory Distress Syndrome

In ARDS model mice, the secretion of S-IgA in intestinal tissues was significantly reduced in the three groups compared to the model group, with the gastrointestinal-lung dual treatment group showing a more pronounced decrease compared to the lung treatment and intestinal treatment groups[16].Yu-Ping-Feng San can improve the reduction of lymphocytes, increase in monocytes and neutrophils, inhibit the expression of pro-inflammatory cytokines and oxidative stress-related mediators, and alleviate pulmonary edema after ALI[17]. Changes in the gut microbiota are also present in the course of ALI/ARDS. Probiotic supplementation therapy has great therapeutic potential. Studies have shown that in ARDS mouse models, gavaging with Lactobacillus rhamnosus or Lactobacillus reuteri can reduce inflammatory cells and mediators in blood and BALF, thereby improving pulmonary vascular permeability and reducing the occurrence of pulmonary edema[18].

2.5 Lung Cancer

There exists a complex network of interactions among lung cancer, gut microbiota, and immunity. In addition, treatment with immune checkpoint inhibitors may alter the composition of the gut microbiota, thereby affecting the efficacy of lung cancer treatment. Metformin regulates the gut microbiota, and improvement in the microbiota composition enhances the efficacy of anti-PD-L1 immunotherapy[19]. Butyrate, a metabolite of the gut microbiota, positively regulates PD-1 expression by modulating the TCR signaling of cytotoxic CD8 T cells, promoting the efficacy of anti-PD-1 immunotherapy[20]. Further research on gut immunity will help deepen our understanding of the pathophysiological mechanisms of lung cancer and provide new ideas and methods for personalized treatment of lung cancer.

3. Conclusion and Prospects

Lung-gut co-treatment, integrating traditional Chinese medicine and modern medical concepts, aims to regulate immune function in patients with pulmonary diseases effectively. By modulating gut microbiota, intestinal mucosal immunity, and immune mediators, lung-gut co-treatment positively influences the immune function of patients with pulmonary diseases, such as COPD, asthma, pneumonia, ARDS, IPF, and lung cancer. Further research is warranted to elucidate the mechanisms underlying the impact of lung-gut co-treatment on immune function in pulmonary diseases and validate its clinical efficacy

and safety, providing scientific evidence for its application in clinical practice.

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