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RESEARCH

A *Lactobacillus* Combination Ameliorates Lung Inflammation in an Elastase/LPS—induced Mouse Model of Chronic Obstructive Pulmonary Disease

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Abstract
Chronic obstructive pulmonary disease (COPD) is the world's leading lung disease and lacks effective and specific clinical strategies. Probiotics are increasingly used to support the improvement of the course of inflammatory diseases. In this study, we evaluated the potential of a lactic acid bacteria (LAB) combination containing *Limosilactobacillus reuteri* GMNL-89 and *Lacticaseibacillus paracasei* GMNL-133 to decrease lung inflammation and emphysema in a COPD mouse model. This model was induced by intranasal stimulation with elastase and LPS for 4 weeks, followed by 2 weeks of oral LAB administration. The results showed that the LAB combination decreased lung emphysema and reduced inflammatory cytokines (IL-1β, IL-6, TNF-α) in the lung tissue of COPD mice. Microbiome analysis revealed that *Bifidobacterium* and *Akkermansia muciniphila*, reduced in the gut of COPD mice, could be restored after LAB treatment. Microbial α-diversity in the lungs decreased in COPD mice but was reversed after LAB administration, which also increased the relative abundance of *Candidatus arthromitus* in the gut and decreased *Burkholderia* in the lungs. Furthermore, LAB-treated COPD mice exhibited increased levels of short-chain fatty acids, specifically acetic acid and propionic acid, in the cecum. Additionally, pulmonary emphysema and inflammation negatively correlated with *C. arthromitus* and *Adlercreutzia* levels. In conclusion, the combination of *L. reuteri* GMNL-89 and *L. paracasei* GMNL-133 demonstrates beneficial effects on pulmonary emphysema and inflammation in experimental COPD mice, correlating with changes in gut and lung microbiota, and providing a potential strategy for future adjuvant therapy.

Keywords COPD · *Lactobacillus* · Gut microbiota · Gut-lung axis · Short chain fatty acids

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by irreversible obstruction of the airways and is associated with an inflammatory disorder of the airways [1, 2]. Several etiological factors, such as cigarette smoking, long-term exposure to air pollution, and pathogenic infections, pose a high risk for the development of COPD [3–5]. Lung parenchymal destruction (emphysema), central airway inflammation (chronic bronchitis), and peripheral airway inflammation (respiratory bronchiolitis) are the pathological hallmarks of COPD [6]. The chronic inflammation of COPD is considered to result from immune cell infiltration and accumulation at the local lung site, with high levels of inflammatory cytokines, including IL-1β, IL-6, TNF-α, and chemokines/chemokine receptors, including CXC chemokine ligand 1 (CXCL1), CXCL8, CXC chemokine receptor 3, triggering lymphoid aggregates, magnifying downstream inflammatory effects, and increasing cytotoxic activity [7–9]. Although several targeted drugs for COPD aim to block lung inflammation—such as infliximab, which blocks TNF-α—current pharmacological therapies still have limited effects and show few valuable results in clinical trials [10, 11].

Changing the gut microbiota through probiotic intervention is closely linked to improvements lung inflammation and injury [12]. Several metabolites or products, including short-chain fatty acids (SCFAs) and amino acids, from the gut microbiota also contribute to respiratory health through the gut-lung axis [13, 14]. Probiotics such as *Lactobacillus*

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