Dysregulated lung commensal bacteria drive interleukin-17B production to promote pulmonary fibrosis through their outer membrane vesicles

With the support by the National Natural Science Foundation of China, the research team directed by Prof. Qian YouCun (钱友存) at Shanghai Institute of Nutrition and Health, Chinese Academy of Sciences, recently reported that lung microbiota and interleukin-17B (IL-17B) are critical for pulmonary fibrosis pathogenesis, which was published in *Immunity* (2019, 50: 692—706).

Mucosal microbiota has been proved to be involved in both the immune homeostasis and diseases of various mucosal tissues. Over the past several years the team has focused on studies about the interactions between mucosal microbiota and interleukin-17 family cytokines. On one hand, disorders of microbiota in colon can drive IL-17C to promote the development of intestinal cancer (Song et al., *Immunity*, 2014); on the other hand, the commensal bacteria in the intestine can also drive IL-17A production to promote intestinal injury repair (Song et al., *Immunity*, 2015). However, people currently know very little about the role of pulmonary microbiota in lung tissue.

Through high-throughput sequencing, the researchers found that there is relatively abundant microbiota in mouse lung tissue under homeostasis, but the microbiota is remarkably disordered during pulmonary fibrosis. Subsequent studies have found that the pulmonary flora can promote the development of pulmonary fibrosis by inducing the expression of IL-17B. Lung microbiota-depleted mice, germ free mice and IL-17B-deficient mice all showed reduced phenotypes of pulmonary fibrosis. Further studies identified that Bacteroides and Prevotella bacteria are significantly elevated during pulmonary fibrosis and can promote IL-17B secretion by secreting OMVs. OMVs are proved to act on TLR2 and TLR4 receptors of alveolar macrophages through components such as lipopolysaccharide and lipoprotein to induce IL-17B production. In turn, IL-17B can directly act on lung epithelial cells to induce the expression of downstream genes to promote the recruitment of neutrophils and the differentiation of Th17 cells, and finally promote the development of pulmonary fibrosis.

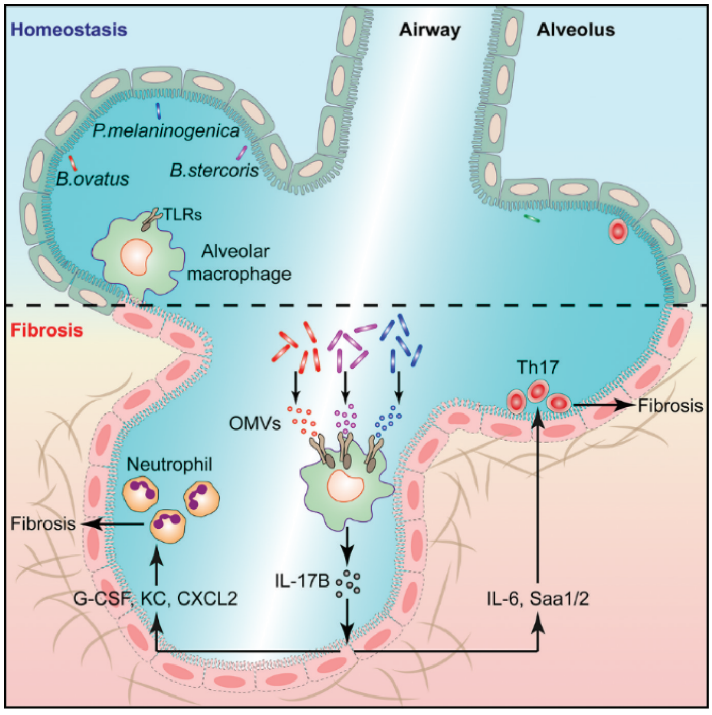

Figure The upregulated pulmonary commensal bacteria can secret OMVs to drive IL-17B production, which can act on epithelial cells to promote the pathogenesis of pulmonary fibrosis.

In summary, the study reveals the function and mechanism of the pulmonary flora in regulating lung mucosa-related diseases, especially pulmonary fibrosis, and provides new ideas and therapeutic targets for clinical treatment of related diseases.