

S1pr1 serves as a viable drug target against pulmonary fibrosis by increasing the integrity of the endothelial barrier of the lung

Jing Jin¹, Mengyao Hao¹, Rong Fu², Juan Tai³, Xia Yuan⁴, Mingjin Wang², Huimin Jiang¹, Ming Ji², Fangfang Lai¹, Nina Xue², Yang Chen⁵, Shuan Rao⁶, Liping Bai⁷, Zhu Yizhun⁷, Xiaoguang Chen², and Xiao-Xi Lv¹

¹Chinese Academy of Medical Sciences & Peking Union Medical College Institute of Materia Medica

²Chinese Academy of Medical Sciences and Peking Union Medical College Institute of Materia Medica

³Department of Otolaryngology, Head and Neck Surgery, Children's Hospital Capital Institute of Pediatrics, Beijing 100020, China.

⁴Peking University School of Pharmaceutical Sciences

⁵Guangzhou University of Chinese Medicine

⁶Southern Medical University Nanfang Hospital

⁷Macau University of Science and Technology

April 13, 2022

Abstract

Background and Purpose: As important components of lung tissue, endothelial cells (ECs) are associated with many lung diseases. The role of ECs dysfunction in idiopathic pulmonary fibrosis (IPF) and how to improve alveolar capillary barrier (ACB) to treat IPF is incompletely understood. Therefore we investigated the involvement of endothelial Sphingosine-1-phosphate receptor 1 (S1pr1) in PF and therapeutic effect of selective S1pr1 agonist IMM002. **Experimental approach:** Databases of IPF patients and individuals without fibrosis were mined by Seurat. We generated an endothelial-conditional S1pr1 knockout (S1pr1^{+/−}) mice and we also examined a bleomycin-induced model of pulmonary fibrosis (PF). We performed qRT-PCR, Western blot, Immunofluorescence staining and EC permeability experiments. **Key results:** Expression of S1pr1 in ECs was reduced markedly in IPF patients. Mice with endothelial-specific S1pr1 deficiency exhibited severer inflammation and fibrosis upon challenge with bleomycin. Significant accumulation of alpha-smooth muscle actin (α -SMA) was observed near vessels after S1pr1 deficiency, which indicated a potential connection between ACB injury and fibrosis. S1pr1 activation by a selective agonist IMM002 could ameliorate PF by improving tight junctions in ECs and protects the ACB. **Conclusion and Implications:** Our results suggest that S1pr1 plays a significant role in ACB and it could be a potential target for IPF. Activation of S1pr1 with IMM002 elicits a potent therapeutic effect in bleomycin-induced fibrosis by increasing tight junctions in endothelial cells and protecting the integrity of ACB therefore improve survival rate and lung function.

Hosted file

6.0+ Main Text File.docx available at <https://authorea.com/users/476071/articles/565146-s1pr1-serves-as-a-viable-drug-target-against-pulmonary-fibrosis-by-increasing-the-integrity-of-the-endothelial-barrier-of-the-lung>



