1. No.
   2017G022

2. Title
   Risk reduction of smoking-related pulmonary fibrosis by adjusting prostaglandin transporter activity

3. Period
   2017-2021

4. Summary

Cigarette smoking is a risk factor of pulmonary fibrosis. Our research demonstrates that prostaglandin transporter SLCO2A1 expressed in alveolar epithelial cells adjust intra and extracellular PGE_2 concentrations; therefore, its reduced expression causes PGE2 stasis in alveolar lumen but a shortage in stromal tissues. Cigarettes smoke extracts (CSE) decreased the expression and function of SLCO2A1 in human and rodent lung epithelial cell models. Moreover, Slco2a1 KO mice showed more severe inflammation and fibrosis when they were treated with bleomycin, and the results were supported by a negative regulation of SLCO2A1 gene expression via by TGF signaling, which is a master regulator of tissue fibrosis. Our results delineate an important role in its antifibrotic activity by transferring PGE_2 released in the alveolar lumen to stromal tissue/cells, which may reduce proliferation and collagen production of fibroblast. Besides, unlike epithelial cells, CSE increased SLCO2A1 expression in endothelial cells, suggesting that it is involved in endothelial to mesenchymal transition (EndMT) because PGE_2 singling suppresses EndMT. Thus, SLCO2A1 expression is regulated in cell-type dependent manner to regulate local PGE2 concentrations precisely. Our results provide an implication that SLCO2A1 is a novel action site of cigarette smoke toxicity in the lungs; however, their relationship needs to be proven in any clinical settings. Phenolsulfonphthalein (PSP), which was found to be a non-metabolic SLCO2A1 surrogate substrate in this study, may be a promising tool to understand the relationship in clinical study. Currently, our achievements in the grant period are published in 11 international peer-reviewed research articles (including 3 reviews), and have been presented in domestic (8 times) and international (6 times) conferences, including 2 invited lectures. In the future, we hope that the knowledge gained will contribute to the development of therapeutic strategies using small chemicals that regulate/adjust SLCO2A1 expression to prevent tobacco-related lung disease.