Transcriptome analysis of bleomycin-induced pulmonary fibrosis in transgenic mice with modifying p38 signal in the lungs: exploration of the novel therapeutic targets for idiopathic pulmonary fibrosis

Matsuda Shuichi¹, Jundal Kim³, Fumihiro Sugiyama⁴, Yuji Matsuo², Junji Ishida³, Kazuya Murata³, Kanako Nakamura⁵, Kana Namiki⁶, Tatsuhiko Sudo⁷, Tomoyuki Kuwaki⁸, Masahiko Hatano¹, Koichiro Tatsumi², Akiyoshi Fukamizu³, Yoshitoshi Kasuya¹,⁶


p38 mitogen-activated protein kinase (MAPK) may contribute to the development of idiopathic pulmonary fibrosis (IPF) through its activation in alveolar epithelial type II cells (AEC II) in response to environmental stresses. We examined whether AEC II-specific genetically modified p38 activity causes worsening of bleomycin (BLM)-induced pulmonary fibrosis and investigated the potential therapeutic targets for IPF progression by assessing its transcriptome. The three mouse genotypes having different p38 activity in AEC II, MKK6-constitutive active, wild type, and p38-dominant negative, received intratracheal administration of BLM and the lungs were analyzed at 8 days post-instillation, known as an active fibrosis phase. Increased histopathological severity, reduced compliance, and higher collagen content of the lungs correlated with increased p38 activity in AEC II. Transcriptome analysis of them revealed that the differentially expressed genes, upregulated by BLM and associated with upregulation of p38 MAPK pathway, were enriched for functions related to endoplasmic reticulum, extracellular matrix, and immune system. Comparison of our data with a publicly available IPF data determined the target genes involved in IPF progression. These findings indicate that p38 MAPK in AEC II plays an important role in IPF progression.