Ferric chloride induces irreversible pulmonary fibrosis in mice

Hidekideki Mikami[1,3], Jundai Kim[4], Shuichi Matsuda[1,3], Keita Ugai[1], Kento Yoshioka[5], Masahiko Hatano[2], Akiyoshi Fukamizu[4], Koichiro Tatsumi[3], Yoshitoshi Kasuya[1]

[1]Department of Biochemistry and Molecular Pharmacology, [2]Department of Biomedical Science, [3]Department of Respirology, Graduate School of medicine, [4]Life Science Center for Survival Dynamics, Tsukuba Advanced Research Alliance (TARA), [5]Departments of Pharmacology

Idiopathic pulmonary fibrosis (IPF) is a fatal respiratory disease with an unknown cause and poor prognosis. To precisely know the pathophysiology of lung fibrotic disease, the appropriate animal model correlating to the pathology of IPF is required. Its establishment may contribute to develop a new strategy for the treatment of patients with IPF. From the transcriptome analysis using lung myofibroblasts derived from the patient with IPF, we found the possible correlation between ferroptosis and lung fibrosis. Then, to investigate whether the intracellular overload of ferrous ion in the lung parenchyma induces fibrotic formation, we subpleurally injected ferric chloride solution into the central part of left upper lobe. Within 1 h post-injection, the intracellular elevation of ferrous ion and ROS was detected by berlin blue and dihydrorhodamine, respectively. At 10 days post-injury, diffuse and severe fibrosis occurred in the whole lung lobe, which was well associated with an excessive collagen deposition, an increase in expression of myofibroblast markers and a decrease in static lung compliance. Likewise, the DNA array/gene set enrichment analysis clearly showed the accumulation of extracellular matrix including collagen in the ferric chloride-injured lung. In our model, it is noteworthy that a prominent hyperplasia of type2 alveolar epithelial cells was observed around the fibrotic lesion and that progressive and irreversible fibrogenesis was verified by a follow-up survey at least for 6 weeks. These features correlate to the pathology of IPF but are not observed in other existing mouse models. In conclusion, we established a new reliable lung fibrosis model.