Department of Internal Medicine
Division of Respiratory Diseases

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General Summary

We performed clinical and basic research concerning chronic obstructive pulmonary disease (COPD), bronchial asthma, pulmonary infection, pulmonary fibrosis, and lung cancer. Basic research should resolve clinical problems, and clinical research should lead to novel treatments. We completed clinical research concerning COPD with the Department of Cardiology and the Department of Diabetes, Metabolism, and Endocrinology. Basic research focusing on the molecular mechanisms of lung injury, fibrosis, and COPD is progressing. We specifically investigated the roles of apoptosis, senescence, and autophagy in the pathogenesis of various lung diseases.

Research Activities

COPD

Clinical research concerning the incidence of COPD in patients with diabetes mellitus, coronary artery diseases, or heart failure has been completed. Serum levels of proinflammatory cytokines, such as tumor necrosis factor and interleukins 1 and 6, were measured in these patients. Oxidative stress was estimated by measuring urine levels of 8-hydroxydeoxyguanosine in patients with COPD. The effect of steroid inhalation on oxidative stress in patients with COPD has been investigated. We concluded that early intervention against COPD may help prevent various comorbidities. We found that the prevalence of COPD in patients with coronary artery disease, heart failure, or diabetes mellitus was higher than that in control subjects. Serum levels of tumor necrosis factor and C-reactive protein decreased in patients treated with statins. Urine levels of 8-hydroxydeoxyguanosine were higher in patients with COPD than in other patients. Clinical research concerning the effects of treatments for COPD, cardiovascular diseases, or diabetes mellitus on comorbidities is continuing. The effects of 1 year of treatment will soon be analyzed.

Infection and Lung injury

A double-stranded RNA virus is associated with acute lung injury. We investigated the effect of insulin on epithelial cell fate after damage by polyinosinic:polycytidylic acid. We used human bronchial epithelial primary culture cells and found that insulin was required to protect these cells from apoptosis induced by polyinosinic:polycytidylic acid. Apoptotic signals were dependent on caspase-8 activation. We also found that survival signals were transmitted mainly through activation of extracellular signal

regulated kinase and v-akt murine thymoma viral oncogene homolog, although other survival signals were also associated. We suggest that insulin is a promising treatment for acute lung injury induced by viral infection. These results were published in *Journal of Immunology*. We are extending this study to investigate the significance of innate immunity on lung injury induced by infection.
We investigated the usefulness of multiplex polymerase chain reaction for detecting the pathogens of pneumonia and infections that trigger the acute exacerbations of COPD and bronchial asthma. We found that the multiplex polymerase chain reaction was more sensitive than conventional tests.

Idiopathic pulmonary fibrosis
Aberrant re-epithelialization with bronchial epithelial cells is a prominent pathologic finding in idiopathic pulmonary fibrosis (IPF) and is implicated in abnormal epithelial-mesenchymal interactions. Recent studies have identified senescence as a risk factor for the development of IPF. Among the SIRT family of class III histone deacetylases (HDACs), SIRT6 has been shown to antagonize senescence. We examined epithelial senescence as a representative phenotypic alteration in conjunction with SIRT6 expression in IPF. We have found evidence that IPF lungs show enhanced senescence with a concomitant increase in SIRT6 expression in epithelial cells, including aberrantly re-epithelialized bronchial cells. We are also investigating the role of autophagy in IPF. We found that autophagy was accelerated in epithelial cells of IPF but that apoptosis and senescence overcome the protective effects of autophagy. These results were published in *American Journal of Physiology Lung Cell and Molecular Physiology*.

Autophagy on bronchiolar epithelial cells
To investigate the significance of autophagy in lung diseases, we examined the association between autophagy and senescence in bronchial epithelial cells. Cigarette smoke extract (CSE) induced senescence in bronchial epithelial cells. We found that CSE transiently upregulated and then downregulated autophagy in these cells. Furthermore, CSE increased missfolded protein and ubiquitinated proteins and induced senescence in these cells. Autophagy digested these unnecessary proteins and protected these bronchial epithelial cells from senescence. Our findings suggest that autophagy plays important roles in maintaining homeostasis in lung epithelial cells. These results were published in *Oncoimmunology* (2012).
In addition, we investigated mitophagy, which specifically targets damaged mitochondria and maintains the homeostasis of mitochondria biogenesis. Mitophagy was consistent with nonspecific autophagy and plays important roles in intracellular homeostasis. We are investigating the roles of mitophagy on the pathophysiology of COPD, IPF, and lung injury.

Lung cancer
Our clinical research on the effects of nitroglycerin on chemotherapy in non-small-cell lung cancer is continuing. This study is a multicenter trial in Japan. A study of the role of endothelial progenitor cells in the progression and treatment of lung cancer is being

planned. We started a clinical study of the effectiveness of TS-1 in elderly patients with non-small-cell lung cancer.

Publications

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Reviews and Books

Fujita Y, Takeshita F, Kuwano K, Ochiya T. RNAi therapeutic platforms for lung diseases. *Pharmaceuticals.* 2012; **6:** 223-50.