Department of Internal Medicine
Division of Respiratory Diseases

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General Summary

We have 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 in collaboration with the Department of Cardiology and the Department of Diabetes, Metabolism and Endocrinology. Basic research focused on the molecular mechanisms of lung injury, fibrosis, and COPD are progressing. We 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 disease, or heart failure has been completed. Serum levels of proinflammatory cytokines, such as tumor necrosis factor, interleukin (IL) 1, and IL-6 were measured in these patients. Oxidative stress in patients with COPD was estimated by measuring urine levels of 8-hydroxydeoxyguanosine. The effect of steroid inhalation on oxidative stress in patients with COPD has been investigated. We hypothesized that early intervention against COPD can prevent various comorbidities. We found that the prevalence of COPD was higher in patients with coronary artery diseases, heart failure, or diabetes mellitus than in control subjects. Serum levels of tumor necrosis factor and C-reactive protein were decreased in patients treated with statins. Urine levels of 8-hydroxydeoxyguanosine in patients with COPD were higher than in other subjects. We are performing clinical research to examine the effects on comorbidities of treatments for COPD, cardiovascular diseases, and diabetes mellitus. We will soon analyze the effects of intervention for 1 year.

Infection and lung injury

Double-stranded RNA viruses are associated with acute lung injury. We investigated the effect of insulin on epithelial cell fate after damage by polyinosinic-polycytidylic acid. Our studies with human bronchial epithelial cells in primary culture found that insulin was required to protect these cells from apoptosis induced by polyinosinic-polycytidylic acid. Apoptotic signals were dependent on activation of caspase 8. We also found that survival signals were mainly through ERK and AKT activation, although other

survival signals may also be associated. We suggest that insulin administration is a promising strategy against acute lung injury induced by viral infection. These results were published in *Journal of Immunology*. We are also investigating the mechanisms of lung injury in influenza virus pneumonia.

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 show that senescence is a risk factor for development of IPF. Among the sirtuin (SIRT) family of class III histone deacetylases, SIRT6 has been demonstrated to antagonize senescence. We examined epithelial senescence as a representative phenotypic alteration in conjunction with SIRT6 expression in IPF. We have obtained evidence that IPF lungs show enhanced senescence with a concomitant increase in SIRT6 expression in epithelial cells, including aberrantly re-epithelialized bronchial cells. Transforming growth factor beta (TGF-β) induces senescence by increasing p21 expression and also induces SIRT6 expression, and artificial overexpression of SIRT6 efficiently inhibits TGF-β-induced senescence via proteasomal degradation of p21. Secretion of IL-β1 from human bronchial epithelial cells induced by TGF-β to become senescent is responsible for myofibroblast differentiation in fibroblasts. These findings shed light on the accelerated epithelial senescence in IPF and on a possible regulatory role for SIRT6. These results were published in *American Journal of Physiology Lung Cell* and *Molecular Physiology*. We are also investigating the role of autophagy in IPF.

Autophagy in 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. Autophagy in these cells was transiently upregulated by CSE but was then downregulated by CSE. Furthermore, CSE increased miss-folded and ubiquitinated proteins and induced senescence in these cells. Autophagy digested these unnecessary proteins and protected these cells from senescence. We suggest that autophagy plays important roles in maintaining homeostasis in lung epithelial cells. These results were published in *Oncoimmunology* (2012).

Lung cancer

Clinical research about the effects of nitroglycerin on chemotherapy in non-small cell lung cancer is going. 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.

Publications

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Reviews and Books

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Kuwano K, Araya J, Hara H. Aging and interstitial lung diseases (in Japanese). *Kokyu to Junkan.* 2011; **59:** 577-85.