Department of Internal Medicine
Division of Respiratory Diseases

Kazuyoshi Kuwano, *Professor*
Katutoshi Nakayama, *Associate Professor*
Jun Araya, *Assistant Professor*
Akira Kojima, *Associate Professor*
Masamichi Takagi, *Assistant Professor*

General Summary

We perform 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 establish novel treatments. We started 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. We specifically investigated the roles of apoptosis, senescence, and autophagy in the pathogenesis of these devastating lung diseases.

Research Activities

COPD

Clinical research concerning the incidence of COPD in patients with diabetes mellitus, coronary artery diseases, or heart failure was performed. Serum levels of proinflammatory cytokines, such as tumor necrosis factor, interleukin (IL) 1, and IL-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 speculated that early intervention against COPD can prevent various comorbidities. We found that the prevalence of COPD in patients with coronary artery diseases, heart failure, or diabetes mellitus was higher than that in control subjects. Serum levels of tumor necrosis factor and C-reactive protein were decreased in patients treated with statins. Urine levels of hydroxydeoxyguanosine in patients with COPD were higher than in other groups. Clinical research is underway concerning the effects on comorbidities of the treatment of COPD, cardiovascular diseases, or diabetes mellitus.

Acute 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. 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 mediated mainly through extracellular signal regulated kinase and Akt activation, although other survival signals may be also associated. We suggest that

insulin administration is a promising strategy against acute lung injury induced by viral infection.

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 members of the nicotinamide adenine dinucleotide-dependent deacetylase sirtuin (SIRT) family, which are class III histone deacetylases (HDACs), 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 produced 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 (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 in human bronchial epithelial cells. Secretion of IL-β1 by human bronchial epithelial cells with TGF-β-induced senescence is responsible for myofibroblast differentiation in fibroblasts. These findings shed light on the accelerated epithelial senescence in the pathogenesis of IPF and a possible regulatory role for SIRT6.

Autophagy and bronchiolar epithelial cells

To investigate the significance of autophagy in lung diseases, we examined the association between autophagy and the senescence of bronchial epithelial cells. Cigarette smoke extract had numerous effects on bronchial epithelial cells: it induced senescence, transiently upregulated and then downregulated autophagy, and increased missfolded protein and ubiquitinated proteins. However, autophagy digested these unnecessary proteins and protected bronchial epithelial cells from senescence. Our results suggest that autophagy plays important roles in maintaining homeostasis in lung epithelial cells. We are also investigating autophagy in pulmonary fibrosis.

Pulmonary infection

We have started to investigate biomarkers for infectious lung diseases. This study focused on the significance of procalcitonin in the diagnosis and treatment of pulmonary infection.

Lung cancer

Clinical research on the effects of nitroglycerin on chemotherapy in non-small cell lung is going. This study is a multicenter trial in Japan. We are planning a study of the role of endothelial progenitor cells in the progression and treatment of lung cancer.

Bronchial asthma

Clinical research concerning the step down of inhalation treatment against bronchial asthma has been started. This study is a prospective, randomized, controlled study. A

manuscript is being prepared for publication.

Publications

Fukumoto J, Harada C, Kawaguchi T, Suetsugu S, Maeyama T, Inoshima I, Hamada N, Kuwano K, Nakanishi Y. Amphiregulin attenuates bleomycin-induced pneumopathy in mice. *Am J Physiol Lung Cell Mol Physiol* 2010; **298:** L131–8.

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