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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 started clinical research concerning COPD 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 role 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 developed. Clinical research was started concerning the effect on comorbidities of intervention for COPD, cardiovascular diseases, or diabetes mellitus. 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 speculate that early intervention against COPD may prevent various comorbidities.

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 (poly IC). We used human bronchial epithelial primary culture cells and found that insulin was required to protect these cells from apoptosis induced by poly IC. Apoptotic signals were dependent on caspase-8 activation. We also found that survival signals occurred mainly through the activation of extracellular signal-regulated kinase and Akt, although other survival signals may also be associated. We suggest that insulin is a promising agent 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 show that senescence is a risk factor for the development of IPF. Among the sirtuin (SIRT) family of proteins, 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 lungs with IPF show enhanced senescence and 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 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 from epithelial cells induced by TGF-β to undergo senescence is responsible for myofibroblast differentiation in fibroblasts. These findings shed light on the accelerated epithelial senescence in the pathogenesis of IPF and suggest a possible regulatory role for SIRT6.

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 induced the senescence of bronchial epithelial cells. Cigarette smoke extract transiently up-regulated autophagy but then down-regulated autophagy in these cells. Cigarette smoke extract increased misfolded proteins and ubiquitinated proteins and induced the senescence of 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.

Pulmonary infection

An investigation of biomarkers for infectious lung diseases was started. This study focused on the significance of procalcitonin in the diagnosis and treatment of pulmonary infection.

Lung cancer

Clinical research into the effects of nitroglycerin on chemotherapy in non-small cell lung is ongoing. 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

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.

Publications

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