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General Summary

We perform clinical and basic research concerning chronic obstructive pulmonary disease (COPD), bronchial asthma, pulmonary infection, pulmonary fibrosis, and lung cancer, which are closely associated with aging. We investigate the pathophysiology of lung diseases associated with aging, especially COPD and idiopathic pulmonary fibrosis (IPF), and the pathogenesis concerning cellular senescence and autophagy. We also collaborate with National Cancer Research Center concerning the detection of mutations of the epidermal growth factor receptor gene (*EGFR*), extracellular vesicles, and immune checkpoint inhibitors in the field of lung cancer treatment.

Research Activities

COPD

The condition known as COPD is caused by the noxious effects of tobacco smoke, which leads to airway epithelial cell injury and the induction of phenotypic changes Such changes as squamous metaplasia and cellular senescence are assumed to be part of the adaptive response to toxic components. Autophagy is a bulk degradation pathway for cellular components which is essential for the maintenance of cellular homeostasis. When autophagy is impaired, damaged proteins and organelles accumulate and lead to cell death and cellular senescence. Cell death and cellular senescence are believed to be involved in the pathogenesis of COPD.

Mitochondria are dynamic organelles that are essential for cellular metabolic functions and continuously change their shape through fission and fusion. The proper regulation of mitochondrial dynamics is crucial for the maintenance of functional mitochondria and, hence, the disruption of dynamics induces excessive reactive oxygen species production, resulting in apoptosis, necroptosis, and cellular senescence. We reported that expression of PINK1/PARKIN, which mediate mitophagy, were decreased in lung epithelial cells from patients with COPD, and that PARKIN knockout mice were susceptible to the development of emphysema in a mouse model of smoking-induced COPD. We also reported that lamin B1 expression of bronchial epithelial cells was decreased in specimens from patients with COPD and was decreased and resulted in cellular senescence in a mouse model of smoking-induced COPD.

Bronchial Asthma

Because most evidence regarding postoperative pulmonary complications had been established more than 10 years ago, we have recently evaluated perioperative management using new inhalant drugs in patients with COPD and asthma. We reviewed physiological backgrounds, surgical factors, and perioperative-specific treatment for COPD and asthma. Risk factors for postoperative pulmonary complications are a history of smoking and severe asthma in patients with asthma and are age, upper abdominal surgery, and long operation time in patients with COPD. Therefore, these complications could be reduced by adequate treatment with inhaled corticosteroids in patients with eosinophilic asthma and by introducing treatment for COPD in patients with COPD.

IPF

We have produced evidence that lungs with IPF show enhanced epithelial cell senescence, including aberrantly re-epithelialized bronchial cells. Playing an important regulatory role in cellular senescence and differentiation is autophagy. We have also found that insufficient autophagy is a potent underlying pathology of both accelerated cellular senescence and myofibroblast differentiation in IPF. Insufficient mitophagy leads to the accumulation of injured mitochondria, which produce excessive reactive oxygen species.

Alveolar epithelial cell (AEC) injury leading to cell death is involved in the process of fibrosis. The excessive apoptosis of AECs has been widely implicated in the pathogenesis of IPF. Necroptosis is a type of regulated/programmed necrosis. A key regulatory role in initiating necroptosis is played by a multiprotein complex composed of receptor-interacting protein kinases (RIPKs) 1 and 3. We found that expression levels of RIPK3 were increased in lungs with IPF and that both apoptosis and necroptosis were detected mainly in AECs. Treatment with bleomycin induced RIPK3 expression in AECs and increased levels of high mobility group box 1 and interleukin 1β in the lungs of mice. Bleomycin-induced lung inflammation and fibrosis were attenuated in RIPK3 knockout mice with a concomitant reduction in high mobility group box 1 and interleukin 1β. Therefore, we concluded that RIPK3-regulated necroptosis in AECs is involved in the mechanism of lung fibrosis development through the release of damage-associated molecular patterns as the pathogenesis.

We also reported interstitial pneumonia associated with psoriasis, which is a chronic and recurrent inflammatory skin disease. Inflammatory processes might extend outside the skin and affect the lungs. We clearly demonstrated the relationship of psoriasis and interstitial pneumonia.

Lung cancer

Noninvasive monitoring of EGFR mutations conferring sensitivity and resistance to tyrosine kinase inhibitors (TKIs) is vital for the efficient treatment of lung adenocarcinoma. Although plasma circulating cell-free tumor DNA can be detected at an early stage, the size of the tumor does not strongly correlate with the concentration of whole cell-free DNA, including normal leucocyte DNA. The analysis of cell-free DNA from patients with acquired TKI-resistance disease or extrathoracic disease has shown that progression is correlated with a high detection rate of TKI-sensitive mutations. We concluded that

cell-free DNA in patients with EGFR-TKI-resistance or extrathoracic disease progression might be useful for the analysis of cancer genomics.

Biomarkers are urgently required for predicting the effects against non-small-cell lung cancer of monoclonal antibodies acting as immune-checkpoint inhibitors against programmed cell death (PD) 1 and PD-L (PD ligand) 1. We investigated the significance of the plasma level of soluble (s) PD-L1 being used as a biomarker for the therapeutic effects of nivolumab, an anti-PD-1 monoclonal antibody. The baseline plasma sPD-L1 concentration was determined with an enzyme-linked immunosorbent assay. A complete or partial response was achieved by 59% of 39 patients with low plasma sPD-L1 levels and by 25% of those with high plasma sPD-L1 levels. In addition, progressive disease developed in 22% of patients with low plasma sPD-L1 levels and 75% of those with high plasma sPD-L1 levels. The time to failure and overall survival were significantly longer for patients with low plasma sPD-L1 levels than for patients with high plasma sPD-L1 levels. The clinical benefit from nivolumab therapy was significantly associated with baseline plasma sPD-L1 levels. Plasma sPD-L1 levels might represent a novel biomarker for predicting the efficacy of nivolumab therapy against non-small-cell lung cancer.

Extracellular vesicles in lung diseases

Extracellular vesicles (EVs), such as exosomes, play an important role in intercellular communication. Recently, the involvement of EVs in the pathogenesis of lung diseases have been examined. The EVs include numerous DNA, proteins, messenger RNAs, and microRNAs that can regulate intercellular communication. Various kinds of respiratory cells release EVs that can have protective or detrimental functions, depending on the type of donor cells, type of stimuli, and components. In lung cancer, tumor-derived EVs carry multiple immunoinhibitory signals, disable antitumor immune effector cells, and promote tumor escape from immune control. The EVs can also maintain airway homeostasis, induce proinflammatory effects, and promote antigen presentation, thereby regulating lung inflammation and immune responses. Therefore, EVs play important roles in the pathophysiology of inflammatory lung diseases. We have addressed the role of EVs in the pathogenesis of asthma, COPD, and IPF and in the treatment of lung cancer.

Publications

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