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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) pathogenesis concerning cellular senescence and autophagy. We also collaborate with the National Cancer Research Center concerning extracellular vesicles in various lung diseases and immune checkpoint inhibitors in the treatment of lung cancer.

Research Activities

Chronic obstructive pulmonary disease

The condition known as COPD is caused by the noxious inhalation of tobacco smoke, which leads to airway epithelial cell injury and inflammation, and the phenotypic changes. Such changes as squamous metaplasia and cellular senescence of epithelial cells 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.

Ferroptosis is a necrotic form of regulated cell death mediated by phospholipid peroxidation in association with free iron-mediated Fenton reactions. Disrupted iron homeostasis resulting in excessive oxidative stress has been implicated in the pathogenesis of COPD. Our *in vivo* and *in vitro* models show labile iron accumulation and enhanced lipid peroxidation with concomitant nonapoptotic cell death during cigarette smoke exposure. Treatment with deferoxamine and ferrostatin 1, in addition to peroxidase (GPx) 4 knockdown, illuminate the role of ferroptosis in cigarette-smoke-treated lung epithelial cells. Nuclear receptor coactivator 4 (NCOA4)-mediated ferritin selective autophagy (ferritinophagy) is starts during ferritin degradation in response to cigarette smoke treatment. Models of cigarette smoke exposure, using both GPx4-deficient and overexpressing mice, clarify the pivotal role of GPX4-regulated cell death during COPD. These findings support a role for cigarette smoke-induced ferroptosis in the pathogenesis of COPD.

Bronchial asthma

Mepolizumab, an anti-interleukin 5 monoclonal antibody, is effective for patients with

severe eosinophilic asthma who show exacerbation or require systemic corticosteroid maintenance therapy. To elucidate the predictive factors of the response to mepolizumab for patients with severe eosinophilic asthma. To determine the predictive factors, we reviewed patient characteristics, comorbidities, biomarkers, pulmonary function, maintenance dose of systemic corticosteroids, and the number of exacerbations in 28 patients with bronchial asthma treated with mepolizumab. The response rate to mepolizumab treatment was 70%. Compared with 11 patients without eosinophilic chronic rhinosinusitis (ECRS), 16 patients with ECRS showed significantly improved systemic corticosteroid-sparing effects, change from baseline FeNO, and symptoms. Multivariate logistic regression analysis identified ECRS as a predictive factor of the response to mepolizumab. Both groups of patients showed improved symptom scores and a decreased number of exacerbations. Mepolizumab substantially improved the clinical variables of patients with eosinophilic asthma complicated with ECRS.

Idiopathic pulmonary fibrosis

We have produced evidence that lungs with IPF show enhanced epithelial cell senescence, including aberrantly re-epithelialized bronchial cells. Playing important regulatory roles 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.

The imbalanced redox status in lung has been widely implicated in IPF pathogenesis. To regulate redox status, hydrogen peroxide must be adequately reduced to water by GPx. Among GPx isoforms, GPx4 is a unique antioxidant enzyme that can directly reduce phospholipid hydroperoxide. We sought to examine the involvement of GPx4-modulated lipid peroxidation in regulating transforming growth factor (TGF) β-induced myofibroblast differentiation. Immunohistochemical evaluations for GPx4 and lipid peroxidation were performed in IPF lung tissues. Immunohistochemical evaluations showed reduced GPx4 expression levels accompanied by increased 4-hydroxy-2-nonenal in fibroblastic focus in IPF lungs. The TGF-β-induced myofibroblast differentiation was enhanced by GPx4 knockdown with concomitantly enhanced lipid peroxidation and SMAD2/SMAD3 signaling. Heterozygous GPx4-deficient mice showed enhancement of bleomycin-induced lung fibrosis, which was attenuated in GPx4-transgenic mice in association with lipid peroxidation and SMAD signaling. These findings suggest that increased lipid peroxidation resulting from reduced GPx4 expression levels may be causally associated with lung fibrosis development through enhanced TGF-β signaling linked to myofibroblast accumulation of fibroblastic focus formation during IPF pathogenesis.

Lung cancer

Prostaglandin E2 (PGE2) is metabolized to prostaglandin E-major urinary metabolite (PGE-MUM). We aimed to elucidate the clinical usefulness of measuring PGE-MUM as an indicator of tumor burden in patients with lung adenocarcinoma. PGE-MUM was measured by a radioimmunoassay in control healthy volunteers (n = 124) and patients with lung adenocarcinoma (n = 54). The PGE-MUM levels were significantly elevated in

patients with lung adenocarcinoma. A PGE-MUM level of 14.9 μg/g·Cr showed 70.4% sensitivity and 67.7% specificity for the diagnosis of lung adenocarcinoma. PGE-MUM levels tended to be positively correlated with cancer progression as determined by the TNM staging system. Advanced stage (stage III, stage IV, and recurrence) was significantly associated with high PGE-MUM levels by logistic regression analysis. No apparent correlation was demonstrated between PGE-MUM and carcinoma embryonic antigen (CEA) levels. PGE-MUM can be a promising biomarker reflecting the systemic tumor burden of lung adenocarcinoma.

Publications

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Reviews and Books

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