

David Kling**Massachusetts General Hospital****Role of MAP Kinases in COPD and IPF**ABSTRACT I

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death in the United States and is a major cause of mortality throughout the world. Although, cigarette smoking is the most common agent of COPD, other lung irritants including pollution, dust, and/or chemicals, can contribute to COPD development. Lungs from patients with COPD have reduced elasticity, damaged alveoli, and inflamed airways filled with mucous. Idiopathic Pulmonary Fibrosis (IPF) is a condition in which deep lung tissue becomes thick and rigid and/or scarred, over time, severely compromising gas exchange and ultimately leading to respiratory failure and death. Approximately 50,000 new cases are diagnosed each year affecting the 50 to 75 years of age cohort; survival is only 3 to 5 years post-diagnosis. IPF is often associated with pulmonary arterial hypertension, heart failure, pulmonary embolism, pneumonia, and/or lung cancer. The specific cellular and molecular abnormalities in the lung that correlate with disease severity or outcome are not well characterized.

The mitogen activated protein (MAP) kinases represent a set of critical signaling pathways in pulmonary growth, development, and homeostasis. The three most widely characterized MAP kinase cascades include the classical mitogen activated protein (MAP) kinase (ERK1/2), the stress activated protein kinase/c-Jun N-terminal protein kinase (JNK), and p38 enzymes. These pathways can be activated by multiple stimuli including growth factor-coupled receptor tyrosine kinases, G-protein coupled receptors (GPCRs), and toxins. Constitutive and/or aberrant activation of MAP kinases contributes to several COPD-associated phenotypes, including mucus overproduction and secretion, inflammation, cytokine expression, apoptosis, T cell activation, matrix metalloproteinase production, and fibrosis. Thus, we hypothesize that these MAP kinase pathways are altered in the pathogenesis of COPD and IPF. To determine if there are both global and/or regional specific aberrant enzyme activation states (hyperactive or hypoactive) in COPD and IPF lungs, western blot analysis and double label fluorescent immunohistochemistry (IHC) will be carried out. Western blot analysis of protein extracts from lungs with COPD, IPF, and healthy tissues will be compared using P-ERK1/2-, P-JNK-, and P-p38-specific antibodies in conjunction with ERK1/2, JNK, and p38 total protein antibodies. Colocalization of enzymatic activities with specific cell types will be carried out by IHC with the following cell-specific-antibody markers: fibroblasts (vimentin); hematopoietic cells including endothelial cells (CD31), erythrocytes (CD71), platelets (PDGF β), macrophages (isolectin B4 and CD31); epithelial cells (TTF1, FoxA2, and T1 α), ciliated epithelial cells (β -tubulin); Clara cells (CC-10), smooth muscle cells (α -smooth muscle actin), mesothelial cells (mesothelial-specific antibodies); and extracellular matrix, (collagen III and fibronectin). Characterization of the activity states in the diseased tissue as well as localization of specific cell types that with aberrant MAP kinase signaling will facilitate development of specific pharmacological targets treat these deadly diseases.