European Respiratory Society
Annual Congress 2013

Abstract Number: 1081
Publication Number: P246

Abstract Group: 3.3. Mechanisms of Lung Injury and Repair
Keyword 1: COPD - mechanism **Keyword 2:** Lung injury **Keyword 3:** No keyword

Title: Involvement of asparatic acid racemization and isomerization in the pathogenesis of COPD

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Body: Background: Oxidative stress induces racemization and isomerization of asparatic acid such as a change from the L-form to D-form which causes a semi-permanent protein transformation. Objectives:We hypothesized that proteins modified and damaged by oxidative stress including amino acid racemization and isomerization might obtain antigenicity as abnormal proteins resulting in immunological inflammation in the airways of COPD. To prove this hypothesis, we investigated abnormal proteins containing D-form aspartic acids in lung tissue from COPD patients. Methods: Lung specimens surgically isolated from COPD patients were utilized to detect D-asparatic acid. To investigate exhaustively D-asparatic acid isomerization in the protein, we employed a paenidase I, D-asparatic asic specific endopeptidase, in combination with comparative two dimensional electrophoresis analysis. The endopeptidase sensitive proteins revealed decreased amounts of intensity in the proteins. The sensitive proteins were identified by mass spectrometry analysis. Furthermore, we studied the asparatic acid isomerization in vitro using a cell culture system under cigarette smoke exposure. Results:In the proteins from COPD lungs, 4 isomerized proteins, Prohibitin, Peroxiredoxin-2, Glutathione S-transferase Pi, and serum amyloid p component, were detected significantly at 30-40% compared to 7% in control patients. Further, in the in vitro studies, cigarette smoke extracts increased the ratio of the isomerized proteins. Concludion: Protein isomerization process occurred highly in the lung of COPD and the content of D-aspartic acid in the proteins of lung tissues from COPD patients was markedly higher than that in normal lungs.