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Title: Lipid mediator levels evidence gender-specific increases in bronchoalveolar lavage fluid of COPD patients relative to healthy smokers

Prof. Craig 25354 Wheelock craig.wheelock@ki.se [1], Dr. David 25355 Balgoma david.balgoma@ki.se [1], Prof. Johan 25356 Grunewald johan.grunewald@ki.se MD [2], Prof. Anders 25357 Eklund anders.eklund@ki.se MD [2], Prof. Magnus 25358 Skold magnus.skold@ki.se MD [2] and Prof. Asa 25368 Wheelock asa.wheelock@ki.se [2]. [1] Medical Biochemistry and Biophysics, Karolinska Institute, Stockholm, Sweden, 17177 and [2] Medicine, Karolinska Institute, Stockholm, Sweden, 17177 .

Body: Chronic obstructive pulmonary disease (COPD) is a leading cause of mortality and morbidity worldwide, which is increasing particularly among females. Lipid mediators (e.g., eicosanoids) have key roles in the pathology of the inflammatory process in the lower airways. Bronchoalveolar lavage fluid (BALF) was obtained from healthy never-smokers, non-symptomatic smokers, and COPD patients of GOLD stage I-II of both genders (20 per group, n=120). A mass spectrometry method was developed to quantify 85 lipid mediators derived from the cytochrome P450 (CYP), lipoxygenase (LOX) and cyclooxygenase (COX) pathways in BALF. An orthogonal projections to latent structures (OPLS) analysis of female COPD vs. female smokers gave the strongest model (CV-ANOVA p=8.6*10-6, R2=0.59, Q2=0.57.), with 9 lipids driving the model. Six of these lipids were from the linoleic acid pathway, including the CYP-derived epoxides and their downstream diol metabolites. Three of the lipids were derived from arachidonic acid via the thromboxane synthase pathway. These 9 lipids strongly correlated with lung function (FEV1; R2=0.91). mRNA levels of genes responsible for the lipid mediator synthesis also correlated strongly with FEV1 (R2=0.84). The principal pathway affected was CYP metabolites of linoleic acid, which includes leukotoxin/isoleukotoxin (9(10)-EpOME, 12(13)-EpOME) and leukotoxin-diol/isoleukotoxin diol (9,10-DiHOME, 12,13-DiHOME). These compounds have been previously found to be increased in acute respiratory distress syndrome (ARDS) patients, suggesting that female COPD patients have distinct markers of pulmonary damage that could offer gender-specific treatment strategies.