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Title: Krüppel-like zinc finger proteins in end-stage COPD lungs with and without severe alpha1-antitrypsin deficiency

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Body: Chronic obstructive pulmonary disease (COPD) is influenced by environmental and genetic factors. An important fraction of COPD cases harbor a major genetic determinant, inherited ZZ (Glu342Lys) α1-antitrypsin deficiency (AATD). Severe, ZZ AATD is associated with a predisposition to early onset, rapidly progressive COPD where emphysema is a major component. We hypothesized that gene expression pattern differs in end-stage COPD with and without AATD. Tissues from explanted lungs of end-stage AATD-related (ZZ, n=3, never treated with AAT augmentation therapy) and “normal” (MM, n=3) COPD were used for microarray gene expression analysis. A total of 162 genes were found to be differentially expressed (p-value ≤ 0.05 and |FC| ≥ 2) between MM and ZZ COPD patients. Of those, 134 gene sets were up-regulated and 28 were down-regulated in ZZ relative to MM lung tissue. A subgroup of genes, zinc finger protein 165, snail homolog 1 (Drosophila), and Krüppel-like transcription factors (KLFs) 4 (gut), 9 and 10, perfectly segregated ZZ and MM COPD patients. The relative expression of KLF 9 and 10 was higher in lung and in liver cirrhosis tissue from ZZ (n=6) compared to MM (n=6) as verified by RT-PCR. Genes associated with COPD or lung function decline generally come from three groups:

protease-antiprotease, oxidant/antioxidant and immune/inflammatory mediators. In this small cohort, we show that end-stage COPD patients with and without AATD can be perfectly grouped by the cluster of the zinc-finger family of transcriptional regulators. Our data provide new insight into the putative difference in the mechanisms involved in COPD development in subjects with and without inherited AATD.