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α_1 Antitrypsin therapy modulates the neutrophil membrane proteome and secretome

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ABSTRACT Obstructive pulmonary disease in patients with α_1 antitrypsin (AAT) deficiency (AATD) occurs earlier in life compared with patients without AATD. To understand this further, the aim of this study was to investigate whether AATD presents with altered neutrophil characteristics, due to the specific lack of plasma AAT, compared with non-AATD COPD.

This study focussed on the neutrophil plasma membrane and, by use of label-free tandem mass spectrometry, the proteome of the neutrophil membrane was compared in forced expiratory volume in 1 s (FEV_1)-matched AATD, non-AATD COPD and in AATD patients receiving weekly AAT augmentation therapy (n=6 patients per cohort). Altered protein expression in AATD was confirmed by Western blot, ELISA and fluorescence resonance energy transfer analysis.

The neutrophil membrane proteome in AATD differed significantly from that of COPD as demonstrated by increased abundance and activity of primary granule proteins including neutrophil elastase on the cell surface in AATD. The signalling mechanism underlying increased degranulation involved Rac2 activation, subsequently resulting in proteinase-activated receptor 2 activation by serine proteinases and enhanced reactive oxygen species production. *In vitro* and *ex vivo*, AAT reduced primary granule release and the described plasma membrane variance was resolved post-AAT augmentation therapy *in vivo*, the effects of which significantly altered the AATD neutrophil membrane proteome to that of a non-AATD COPD cell.

These results provide strong insight into the mechanism of neutrophil driven airways disease associated with AATD. Therapeutic AAT augmentation modified the membrane proteome to that of a typical COPD cell, with implications for clinical practice.