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Title: Effect of human neutrophil proteases on ex vivo small airway function

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Body: Small airways are the main site of airflow obstruction in COPD. Neutrophils are implicated in COPD pathophysiology via the activity of their released products, including proteases, which damage airway tissue. We studied the effects of activated neutrophil supernatants on small airway function in rat precision-cut lung slices (PCLS) using videomicroscopy. PCLS were incubated overnight in fMLP-stimulated neutrophil supernatants from non-smokers (NS), smokers (S) and COPD patients (C), and contraction to carbachol (CCh) assessed. Supernatant levels of MMP-8, -9, neutrophil elastase (NE) and myeloperoxidase (MPO) were measured. Compared with untreated (UT) airways, airway maximal contraction (at 10μM CCh) was significantly reduced after incubation in supernatants (UT 80±4; NS 56±10; S 40±11; C 52±7%, n=6-10, $p<0.01$). Airway reopening after CCh washout was significantly augmented in airways incubated in neutrophil supernatants, compared with UT airways (UT 18±8; NS 157±25; S 186±68; C 171±79% difference in contraction (10μM CCh vs. post-washout), n=4, $p<0.05$). There was a significant decrease in baseline airway patency after incubation in COPD neutrophil supernatants, compared with UT airways (10±5 vs. 40±7% decrease in patency, n=8-10, $p<0.01$). Maximal contraction correlated with supernatant [NE] ($r=-0.5$, n=46, $p<0.001$) and [active MMP-9] ($r=-0.6$, n=27, $p<0.001$), whilst airway reopening correlated with [NE] ($r=0.6$, n=11). Hence, activated neutrophil supernatants reduce maximal contraction, augment reopening, and decrease baseline patency of small airways, possibly due to proteolytic action. Thus, increased numbers of neutrophils in COPD may contribute to the airway dysfunction characteristic of the disease.