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Title: Sputum neutrophil mediators in experimental rhinovirus infection in COPD

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Body: Background. Acute exacerbations of COPD (AECOPD) are associated with neutrophilic airway inflammation. Inhibition of TNF- α was recently found to be ineffective in AECOPD. We used experimental rhinovirus (RV) infection to investigate neutrophil chemokines in AECOPD. Methods. 9 COPD subjects, 9 smokers (SMK) and 8 non-smokers (NS) were successfully infected with RV. Induced sputum (IS) was collected prior to infection and on days 3, 5, 9, 12, 15, 21 and 42 post-infection. Levels of IL-8, GM-CSF, IL-1 β , TNF- α , GRO- α and MMP-9 were measured in IS supernatants using the Meso Scale Discovery (MSD®) platform. Results. MMP-9, IL-8, GM-CSF, IL-1 β , and TNF- α in IS increased significantly from baseline following RV infection in the COPD group but not in the SMK or NS, GRO- α was not induced. Peak levels correlated with inflammatory cell counts, neutrophil numbers and neutrophil elastase (NE) in IS in the COPD subjects.

	Sputum NE	Sputum TCC	Sputum Neutrophils	TNF- α	IL-8	GM-CSF	IL-1 β
TNF- α	P=0.0007, r=0.93	P=0.025, r=0.73	P=0.0016, r=0.77	X	NS	P=0.0025, r=0.87	P=0.0072, r=0.82
IL-8	P=0.04, r=0.68	P=0.0096, r=0.8	P=0.0072, r=0.82	NS	X	NS	P=0.0072, r=0.82
GM-CSF	P=0.016, r=0.77	P=0.016, r=0.77	P=0.02, r=0.75	P=0.0025, r=0.87	NS	X	NS
IL-1 β	P=0.03, r=0.72	NS	P=0.036, r=0.7	P=0.0072, r=0.82	P=0.0072, r=0.82	NS	X
MMP-9						NS	

P=0.02, r=0.75	P=0.016, r=0.88	P=0.025, r=0.87	P=0.0025, r=0.87	P=0.049, r=0.87	P=0.03, r=0.72
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Conclusions. IL-8, GM-CSF, IL-1 β , and TNF- α , but not GRO- α , are all involved in neutrophilic inflammation in AECOPD. Inhibition of single cytokines is unlikely to be successful in AECOPD. High levels of the protease MMP-9 are induced so NE inhibition may also be unsuccessful. Therapeutic strategies that target multiple chemokines or multiple proteases are likely to be required in AECOPD.