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Title: Effect of cigarette smoking on sputum proteomic profiles in patients with asthma and healthy volunteers

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Body: Background: Smokers with asthma have more severe symptoms and impaired short-term therapeutic response to corticosteroids, but the mechanisms accounting for these adverse effects are poorly understood. We hypothesize that the differences in sputum protein profiles provide insight into the pathophysiological effects of smoking in asthma. Methods: High resolution label-free shotgun proteomics was employed to investigate sputum protein profiles in 43 asthmatic non-smokers, 50 asthmatic smokers, 10 healthy non-smokers and 10 healthy non-smokers. Protein expression was normalized to sputum albumin level. Results: A total of 596 and 335 proteins were confidently detected (FDR<1%, Mascot) in asthmatic patients and healthy volunteers, respectively. Among them, 73 and 68 proteins were found differentially expressed between smokers and non-smokers for asthmatic patients and healthy volunteers, respectively ($p<0.05$, Benjamini corrected). Majority of differences observed were up-regulation in smokers. Functional enrichment analysis shows that peptidase inhibitor activity and acute inflammatory/defence response were over-representative in healthy smokers compared to healthy non-smokers ($p<0.05$, Benjamini corrected). In asthmatic smokers, there was an over-representation of oxidoreductase activity, thioredoxin fold (glutathione S-transferase), response to extracellular stimuli and lysosome related peptidase activity. Conclusions: These results suggest that asthmatic patients may be hyper-responsive to cigarette smoke and that their airways may be susceptible to potential damage from lysosome related peptidase activity.