Journal Highlight: Mucus plugs in patients with asthma linked to eosinophilia and airflow obstruction

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It is currently unclear if eosinophilic inflammation in asthma directly causes airway hyper-responsiveness (AHR), airflow obstruction and thereby symptoms. One possibility is that eosinophilic degranulation alters smooth muscle function, rendering it hyper-responsive and thus could be considered an extra-luminal cause of variable airflow obstruction. However, another possibility is that eosinophilic degranulation in the lumen of the airways contributes to excess mucus production resulting in luminal obstruction, independent of AHR. This mucus production is evident and well-described in *acute* severe, often life-threatening asthma, but it might also be an important cause of airflow obstruction in *chronic* uncontrolled asthmatics, who despite aggressive inhaler therapy have persistent symptoms, fixed airflow obstruction and show only a modest reversibility to bronchodilators.

Dunican et al (1) recently addressed this question in patients with chronic severe asthma in work published in the June 2018 issue of the Journal of Clinical Investigation. In an elegant study design that included a systematic method of quantifying mucus plugs in 20 sub-lobar segments using CT scans, they showed i) mucus plugs occurred in at least 1/20 segments in 58% of asthmatics compared with only 4.5% of health controls; ii) a high mucus plug score (≥4 segments affected) was found in two-thirds of asthmatics who had the lowest lung function (FEV1<60% predicted) and airflow obstruction persisted despite treatment with bronchodilators and intramuscular triamcinolone; iii) plugs were associated with marked increases in sputum eosinophils and eosinophil peroxidase (EPO). Furthermore, in a cohort of patients who had two CT scans 2-9 years apart, they found 90% of patients had persistent mucus plugs and 65% of the same lung segments were affected. Finally, they provide evidence in an ex-vivo gel model to show that EPO catalyses the reaction between hydrogen peroxidase and thiocyanate resulting in hydroisocyanate and this product has the ability oxidize the thiol groups on cysteine residues thereby making the mucus stiffer and presumably more difficult to clear.

The clinical implication of this study is that persistent uncontrolled symptoms may be due to a luminal or extra-luminal cause, and both these areas need to be targeted for effective treatment control. This may involve optimizing an anti-type 2 inflammatory approach or as this new study suggests, perhaps a targeted anti-mucus approach. With regards to the findings of this paper, Professor Param Nair from McMaster University commented, *"A combination of sputum quantitative cytometry, CT imaging of the airways to identify luminal contents such as eosinophils and mucus, and noble gas MRI ventilation imaging to identify the consequence of this luminal obstruction, could potentially help to specifically target each one of these components individually with anti-IL-5, anti-IL-5 receptor or anti-IL-4/IL-13 mAb respectively."*

Question and Answers with Dr John Fahy (Senior Author):

Imran: Firstly, congratulations on this exciting publication and thank you for you time in engaging in this Q&A session. This was a fascinating paper to read but I was interested to know how your research group came up with the idea of investigating mucus plugs?

Dunican EM, Elicker BM, Gierada DS, Nagle SK, Schiebler ML, Newell JD, et al. Mucus plugs in patients with asthma linked to eosinophilia and airflow obstruction. J Clin Invest. 2018 Mar 1;128(3):997–1009.

Dr John Fahy: My lab has a long-standing interest in mucus pathology in airway disease and we brought this interest to our involvement in the Severe Asthma Research program (SARP). The clinical phenotyping in SARP includes lung imaging and we noticed that the clinical reads on these scans frequently reported mucus plugs as a finding. We decided to quantify the finding by developing a mucus plug score.

Imran: As someone who has a big interest in chronic cough, particularly in subjects with asthma, it was interesting to see that there was no signal whatsoever in patients with chronic mucus hypersecretion. However, do you think that given the persistent airflow obstruction and air trapping, is this is the wrong symptom to identify such patients? Should the focus be more on shortness of breath or exercise capacity as a better indicator?

Dr John Fahy: Yes we too found it interesting that the mucus plugs are clinically silent in many patients. This may be because the plugs largely occur in subsegmental airways where cough receptors are not prevalent. And it also point to the problem of using symptoms of sputum production as a surrogate for mucus pathology in the airways.

Imran: Do you think that the mucus plugs are constantly forming, dissolving and reforming? Or do you think patients can actually cough these plugs up – that in the acute setting, the respiratory therapist can often help clear plugs using physiotherapy techniques? There has been some evidence in the literature of plastic bronchitis; where casts are coughed up or occasionally needing bronchoscopic clearance. Any thoughts on this?

Dr John Fahy: I think of plastic bronchitis as fibrin plugs that occur following an airway bleed. The plugs in our study are mucus plugs that occur persistently in specific airways within a patient. It is not clear why these patients have airways that are susceptible to mucus plugging but the finding that they occur in patients with type 2 high (eosinophilic) pathology suggests that the airways are prone to persistent type 2 inflammation that causes a combination of pathologies that lead to plugs. These pathologies include mucin hypersecretion from mucin gene upregulation and mucin crosslinking from the effects of thiol reactive oxidants that form when an excess oxidative species (e.g. H_2O_2) and halide substrates (e.g. thiocyanate) are acted on by peroxidases such as eosinophil peroxidase. So it's a kind of perfect storm that occurs in focal airways.

Imran: Do you think that currently available biological therapy targeting type 2 inflammation might help prevent mucus plugs? Or do you think we may need to develop therapy specifically targeting the cross-linking of thiol groups?

Dr John Fahy: Yes I think the newly available biologics that target IL-13 and IL-5 should be effective in preventing these plugs but there should also be an effort to develop mucolytics to specifically target these plugs.

Imran: How would you describe the study findings to a non-specialist audience?

Dr John Fahy: We found that mucus plugs are prevalent in chronic severe asthma and may explain chronic airflow limitation in these patients. Treating these plugs is a rational strategy to improve airflow in these patients.

Imran: Thank you very much for your time and effort in this review process.

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