

APSR RESPIRATORY UPDATES



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I. INFLAMMATION IN ASTHMA AND COPD IS HETEROGENEOUS

A large subgroup of mild-to-moderate asthma is persistently noneosinophilic

Authors: McGrath KW et al.

Reference: Am J Respir Crit Care Med. 2012;185:612-9.

URL: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3326288/>

Comments: The airway inflammatory response in asthma has been reported to be heterogeneous in a number of studies. This report from the Asthma Clinical Research Network in the USA found that asthma could be categorised into roughly equal proportions of eosinophilic and noneosinophilic phenotypes. They were reasonably stable, and the eosinophilic phenotype was responsive to corticosteroid therapy whereas the noneosinophilic phenotype was steroid nonresponsive.

Impaired macrophage phagocytosis in non-eosinophilic asthma.

Authors: Simpson JL et al.

Reference: Clin Exp Allergy. 2013;43:29-35.

URL: <http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2222.2012.04075.x/pdf>

Comments: Impaired macrophage clearance of apoptotic cells, termed efferocytosis, has been described in COPD as a mechanism for persistent airway inflammation. In this study, Simpson et al. questioned whether impaired efferocytosis also occurred in asthma. The authors adapted a flow cytometry based efferocytosis assay to use with induced sputum, providing an advance in technique. They found that efferocytosis was impaired in noneosinophilic asthma, similar to COPD, and that this may explain the persistence of neurophilic inflammation in the 2 airway diseases.

New Impact factor and ranking for [Respirology](#) released in June 2013



Edited By: Peter Eastwood

Impact Factor: 2.781

ISI Journal Citation Reports ©

Ranking: 2012: **18/50** (Respiratory System)

Online ISSN: 1440-1843

Sputum inflammatory cell-based classification of patients with acute exacerbation of chronic obstructive pulmonary disease.

Authors: Gao P et al.

Reference: PLoS One. 2013 May 31;8(5):e57678

URL: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3669375/>

Comments: There is also heterogeneity in the inflammatory response in COPD, and as this study shows, during COPD lung attacks. The pattern is different to asthma, with fewer eosinophilic patients and more neutrophilic responses. The neutrophil in COPD seems to modulate clinical expression of the disease. Other studies link airway neutrophilia to reduced FEV1, and this study confirms this and shows that airway neutrophilia is associated with bacterial infection, longer length of hospital stay, and a higher BODE score. The heterogeneity argues for phenotype specific treatment of lung attacks, and the need to specifically target neutrophil responses to improve clinical outcomes.

II. MECHANISMS AND IMPORTANCE OF AIRWAY INFECTION IN COPD

Rhinovirus infection induces degradation of antimicrobial peptides and secondary bacterial infection in chronic obstructive pulmonary disease.

Authors: Mallia P et al.

Reference: Am J Respir Crit Care Med. 2012;186:1117-24.

URL: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3530206/>

Comments: Airway infection with either viruses or bacteria are the major cause of lung attacks. Clinicians often suspect co-infection with bacteria and viruses, but how common this is and exactly how virus infection leads to secondary bacterial infection is not known. The authors of this study were able to prospectively examine this by using experimental rhinovirus infection in patients with COPD. They found that virus-bacterial co-infection was common, occurring in up to 60% of COPD lung attacks. They also established that co-infection occurred due to a disabling of protective antimicrobial defenses in the airways of COPD patients. The study also identified targets for therapy, such as elafin, which could be treated either by replacement or enzyme inhibition.

Microbiome diversity in the bronchial tracts of patients with chronic obstructive pulmonary disease.

Authors: Cabrera-Rubio R et al.

Reference: J Clin Microbiol. 2012 ;50:3562-8.

URL: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3486223/>

Comments: Studies of microbial diversity have identified a rich and dynamic interaction between microbial species and humans. The lung is an active part of this, and whereas the lower respiratory tract was once considered sterile, it is now known to be colonized by many and varied microbial species, termed the microbiome. This study shows that induced sputum techniques have now been adapted to enable sampling of the lung microbiome and species identification using modern molecular techniques. The induced sputum microbiome shows less microbial diversity than other lung compartments, such as the bronchoalveolar space or the airway mucosa. In addition, in COPD, the central airways sampled by induced sputum showed a different species profile to lower airway samples. This study now paves the way for further mechanistic and treatment studies to investigate the significance of airway microbial diversity in COPD.

III. IMMUNE MECHANISMS OF ASTHMA AND COPD

Decreased CTLA4+ and Foxp3+ CD25highCD4+ cells in induced sputum from patients with mild atopic asthma.

Authors: Kawayama T et al.

Reference: Allergol Int. 2013;62:203-13.

URL: http://ai.jsaweb.jp/fulltext/062020203/062020203_index.html

Comments: The importance of T cell control of eosinophilic asthma is well established. However, the mechanisms that regulate T cell responses in asthma continue to be increasingly understood. A new T cell subtype was recently identified that is capable of widespread and powerful suppression of T cell responses, termed Treg cells. It is reasonable to propose that a deficiency of either Treg cell number or function could be involved in the persistent Th2 eosinophilia in asthma. In this study, the authors found that induced sputum Treg cell numbers were lower in asthma, and this abnormality was present even in mild asthma. Changes in Treg cells in asthma may be an important piece of the immune puzzle of this condition.

Airway function, inflammation and regulatory T cell function in subjects in asthma remission.

Authors: Boulet LP et al.

Reference: Can Respir J. 2012 ;19:19-25.

URL: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3299047/>

Comments: Clinicians also recognize patients with asthma who appear to undergo remission of their disease, and this provides a natural experiment to study how asthma might be resolved. Because Treg cells are capable of widespread and powerful suppression of T cell responses, studying the role of these cells in asthma in remission might shed more light on how the immune response regulates clinical asthma. This manuscript reports an evaluation of asthma in remission and finds that even though there was complete remission of symptoms, other markers of disease still remained, such as airway hyperresponsiveness, and eosinophilic inflammation. This was explained by finding a persistence of Treg cell dysfunction, indicating that there was incomplete T cell suppression of eosinophilic inflammation that persisted after clinical remission. This has implications for future risk of asthma recurrence, and for where cell-based immune modulatory treatment might be directed.

Levels of leptin and IL-6 in lungs and blood are associated with the severity of chronic obstructive pulmonary disease in patients and rat models.

Authors: Liang R et al.

Reference: Mol Med Rep. 2013 May;7(5):1470-6.

URL: [http://www.ncbi.nlm.nih.gov/pubmed/?term=Mol+Med+Rep.+2013+May%3B7\(5\)%3A1470-6.](http://www.ncbi.nlm.nih.gov/pubmed/?term=Mol+Med+Rep.+2013+May%3B7(5)%3A1470-6.)

Comments: Leptin is a key cytokine produced by adipose tissue in obesity. Leptin levels are elevated in obesity, asthma, as well as obese asthma. In addition, the lung has abundant leptin receptors, with leptin playing a role in surfactant expression during development. Thus, leptin may be an important pulmonary cytokine, but its role in pulmonary disease is unknown. This study helped address this issue by evaluating leptin in stable and acute COPD. During a COPD lung attack, induced sputum leptin levels were elevated, and in a model system, leptin was localized to both airway epithelial cells and inflammatory cells. Leptin may prove to be an important pulmonary cytokine in lung disease.

Dupilumab in persistent asthma with elevated eosinophil levels.

Authors: Wenzel S et al.

Reference: N Engl J Med. 2013 May 21.

URL: <http://www.nejm.org/doi/full/10.1056/NEJMoa1304048>

Comments: New and effective drug development in asthma is being realized by using monoclonal antibodies to target specific pathways in subtypes of the disease. This approach can achieve spectacular effects when applied to the right subgroup, and yet is completely ineffective if the subgroup is not targeted or underrepresented in the study population. This new approach combines the use of biomarkers to define the subgroup and pairs this with a pathway specific therapy. The above study exemplifies this approach by using eosinophils in blood or sputum to identify the subtype, paired with treatment using dupilimab, a monoclonal antibody against IL4Ra, and showing an 87% reduction in lung attacks from asthma. The consistent success of this approach both validates the importance of recognizing asthma phenotypes, and offers patients with refractory disease effective treatment options.

IV. INDUCED SPUTUM IN LUNG CANCER DETECTION ?

Analysis of aberrant methylation on promoter sequences of tumor suppressor genes and total DNA in sputum samples: a promising tool for early detection of COPD and lung cancer in smokers.

Authors: Guzmán L et al.

Reference: Diagn Pathol. 2012 ;7:87.

URL: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3424112/>

Comments: The major recent advances in cancer therapy have come from the phenotyping of cancers and the recognition of oncogenes and tumor suppressor genes as key targets. These genes can be activated or inactivated[silenced] by methylation of promoter sites in the respective DNA sequence. In this study, molecular methods to detect these changes have been successfully adapted to induced sputum, and the techniques applied to COPD and lung cancer. In lung cancer and COPD, the genes that normally function to suppress tumor growth[tumor suppressor genes] were inactivated[methylated]. Because induced sputum is a simple technique that can be used to sample the airway on repeated occasions, this important finding opens the prospect of using induced sputum as a tool for the early diagnosis of lung diseases. It also highlights the overlap in molecular mechanisms that may explain the raised risk of lung cancer in COPD.



25th
Anniversary of APSR
Respiriology

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Date: **November 11-14, 2013**
Congress Venue: **Pacifico Yokohama**
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Hosted by: **The Japanese Respiratory Society**
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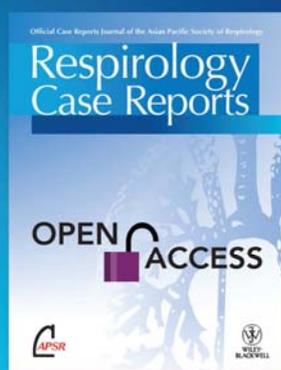
APSR Respiratory Updates is an initiative of the APSR Education Committee

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to attend the

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Asian Pacific Society of Respiriology

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- Contribute to the development of research and science of respiratory medicine in the Asian Pacific region.

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<http://www.apsresp.org/scholarships/2013/apsr01.html>

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