Clinical relevance of genomic signatures of type 2 inflammation in chronic obstructive pulmonary disease

The Dutch hypothesis,[1] proposed by Dick Orie in 1961 at the University of Groningen, provides one of several biologically plausible explanations for the pathogenesis of chronic obstructive pulmonary disease (COPD). Clinical characteristics such as allergy and bronchial hyperresponsiveness that are commonly observed in individuals afflicted with asthma were viewed as likely determinants of COPD. Orie emphasised the interplay of host (genetics, allergy and airway hyperresponsiveness) and environmental (smoking, air pollution and infection) factors, as well as the importance of carefully phenotyping patients to discern the actual critical features of disease in individual patients.

It has since become clear that susceptibility to cigarette smoking, and hence COPD risk, is indeed conferred by pre-existing airway hyperresponsiveness and eosinophilia.[2] Tilley *et al.*[3] reported on a 'COPD-like' small airway epithelial transcriptome; by identifying differentially expressed genes they could classify clinically healthy smokers into subgroups with lesser and greater responses to cigarette smoking. Following these results, whole-genome gene expression profiling done on bronchial biopsies from COPD patients treated with inhaled corticosteroids (ICS) in the GLUCOLD study,[4] showed that gene expression in biological pathways of COPD is dynamic with treatment and reflects disease activity.

This was the background on which Christenson *et al.*[5] recently tested the hypothesis that COPD and asthma could share partially overlapping airway gene expression changes, reflecting shared processes that contribute to airflow obstruction. They compared disease-associated airway epithelial gene expression alterations in an asthma cohort and two COPD cohorts. A subphenotype (endotype) of asthma with increased airway Th2 inflammatory markers, the 'Th2-high' endotype, had higher IL-5 and IL-13 expression levels in bronchial biopsies, increased serum total IgE levels, greater blood and lung eosinophilia, increased airway hyperresponsiveness, and a better lung function (FEV_1) response to ICS.[6] When evaluating this T helper type 2 (Th2) signature score (T2S) in two cohorts of steroid-naive COPD patients, there was significant gene expression overlap. Of the 200 genes most differentially expressed in asthma v. healthy control subjects, the expression of these genes in the COPD cohorts was enriched and associated with more severe airflow obstruction ($p<0.001$). A higher T2S score was associated with decreased lung function ($p<0.001$), but not asthma history, in both COPD cohorts. Higher T2S scores correlated with increased airway wall eosinophil counts ($p=0.003$), blood eosinophil percentage ($p=0.03$), bronchodilator reversibility ($p=0.01$) and improvement in hyperinflation after corticosteroid treatment ($p=0.019$) in GLUCOLD.[4]

Interestingly, from the same institute, Smolonska *et al.*[7] recently performed genome-wide association studies for both asthma and COPD and could find no common single nucleotide polymorphisms that reached genome-wide significance. They did, however, suggest that although inflammatory processes differ in asthma and COPD, they are both mediated by the NF-kB pathway, and could therefore be driven by the same underlying genes.

Half a century later, it would seem that the Dutch hypothesis may indeed hold true but only for a small subset of COPD and asthma patients who co-express similar gene expression alterations. The implications of this work are that genomics may lead the search to find biomarkers that will allow us to categorise patients with COPD into clearly defined clinical groups, and possibly even to novel therapeutics to improve the care of patients with COPD.

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References

1. Orie NGM, Sluiter HJ, De Vries K, Tammeling GJ, Witkop J. The host factor in bronchitis. In: Orie NGM, Sluiter HJ, editors, Bronchitis. Assen, the Netherlands: Royal Van Gorcum; 1961. pp. 43-59.
2. Hospers JJ, Postma DS, Rijcken B, Weiss ST, Schouten JP. Histamine airway hyperresponsiveness and mortality from chronic obstructive pulmonary disease: A cohort study. Lancet 2000;356(9238):1313-1317. [http://dx.doi.org/10.1016/S0140-6736(00)02815-4]
3. Tilley AE, O'Connor TP, Hackett NR, et al. Biologic phenotyping of the human small airway epithelial response to cigarette smoking. PLoS One 2011;6(7):e22798. [http://dx.doi.org/10.1371/journal.pone.0022798]
4. Van den Berge M, Steiling K, Timens W, et al. Airway gene expression in COPD is dynamic with inhaled corticosteroid treatment and reflects biological pathways associated with disease activity. Thorax 2014;69(1):14-23. [http://dx.doi.org/10.1136/thoraxjnl-2012-202878]
5. Christenson SA, Steiling K, van den Berge M, et al. Asthma-COPD Overlap. Clinical relevance of genomic signatures of type 2 inflammation in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2015;191(7):758-766. [http://dx.doi.org/10.1164/rccm.201408-1458OC]
6. Bhakta NR, Solberg OD, Nguyen CP, et al. A qPCR-based metric of Th2 airway inflammation in asthma. Clin Transl Allergy 2013;3(1):24. [http://dx.doi.org/10.1186/2045-7022-3-24]
7. Smolonska J, Koppelman GH, Wijmenga C, et al. Common genes underlying asthma and COPD? Genome-wide analysis on the Dutch hypothesis. Eur Respir J 2014;44(4):860-872. [http://dx.doi.org/10.1183/09031936.00001914]

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