Obesity and allergic asthma are complex processes in which many complementary and synergistic pathways contribute to clinical manifestations of disease. The current article suggests that a common factor can lead to the pathogenesis of both, as well as suggesting the appealing idea that intervention in the Sirt1–Chi3l1 pathway may simultaneously intervene in obesity and allergic asthma. Although pharmacologic approaches are attractive, the effect of dietary manipulation is of great interest. There is precedent to suggest a high-fat diet can affect airway inflammation: Wood and colleagues have reported that a high-fat meal can increase airway neutrophilic inflammation and decrease bronchodilator responsiveness in asthma (16). It will be of great interest to know whether dietary manipulation or other means of weight control could affect allergic asthma outcomes in obese people, analogous to the effects in mice from pharmacologic and genetic approaches targeting the Sirt1–Chi3l1 pathway. ■

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The Dutch Hypothesis Meets Genomics

In 1960, the Dutch pulmonologist N. G. M. Orie organized a conference to discuss the origins of chronic bronchitis (1). Adult pulmonologists recognized that smoking was the major cause of the disease, yet only 15–20% of smokers went on to get chronic bronchitis, as chronic obstructive pulmonary disease (COPD) was called at the time, and the disease was quite heterogeneous, with infection being a prominent component. Orie emphasized the interplay of host (genetics, allergy, and airway hyperresponsiveness) and environmental (smoking, air pollution, infection) factors, as well as the importance of carefully phenotyping patients to discern the actual critical features of disease in individual patients. This subsequently became known as the Dutch Hypothesis. Many investigators have misinterpreted Orie's idea to be that asthma and COPD are the same disease, and his hypothesis was reduced to those who favored splitting asthma and COPD into separate diseases versus the lumpers, who favored calling them the same or a single disease. Ironically, Orie and his Dutch colleagues were considered lumpers, despite his call for careful subphenotyping and subsetting of patients with COPD.

In the 1980s, it became clear that susceptibility to cigarette smoking, and hence COPD risk, was indeed conferred by preexisting airway hyperresponsiveness and eosinophilia, partially vindicating Orie, at least on the importance of these host characteristics in conferring increased risk for COPD, independent of cigarette smoking (2–6). This work also

contributed to today's more sophisticated thinking that COPD is still a very heterogeneous condition in which a significant subset of patients, if well phenotypically characterized, have features of both asthma and COPD and constitute an overlap of the two conditions (7).

This very brief history supplies the context to interpret the article in this issue of the *Journal* by Christenson and colleagues (pp. 758–766), which highlights the identification of a genomic signature for type 2 or Th2 inflammation in COPD (8). An all-star group of asthma/COPD genomicists looked at airway-derived gene expression in an asthma cohort and two COPD cohorts. They had a Th2 gene signature (T2S score) in the asthma cohort, which was informed by prior work in asthma genomics, and they applied that T2S score to the COPD cohorts, finding significant gene expression overlap between asthma and COPD for genes specific for Th2 inflammation. A higher T2S score was associated with decreased lung function, increased airway wall eosinophil counts, blood eosinophil percentage, and both responsiveness to short-acting bronchodilator and inhaled corticosteroids. Most important, the identified genomic signature was not predicted by any clinical feature of asthma or COPD.

The authors note a number of methodological issues with which they had to deal to successfully complete this work. The gene expression samples, although all from airway tissue, were not collected in the same way across their studies. Nor were the gene expression platforms the same, necessitating significant work to standardize the data across the studies. Then they had to deal with multiple comparisons, replication, and residual confounding by population differences across the studies. Despite these challenges, they were successful in identifying a replicating gene signature.

The implications of this work are twofold: first, as the authors state, genomics may lead to novel biomarkers that will allow us to subset patients with COPD into clearly defined clinical groups, and second, these same, or other, biomarkers will lead us to novel therapeutics to improve the care of patients with COPD. I do not think either of these two goals will be fully met without the integration of additional genomics data to this, and other, data sets.

What might be the additional genomic data and the next steps in this genomic journey? I suggest that integrating microRNA data with the gene expression data would be one fruitful way to go. MicroRNAs are epigenetic controllers of gene function that are transcriptional repressors (9). Importantly, they are secreted by cells in exosomes and attached to serum proteins (10). In this way, they control cell–cell and organ-to-organ signaling. The most common way to obtain microRNA data has been via RNAseq in the relevant tissue (11). Recently, and most important, it has been shown that microRNAs are stable in serum and plasma and, when measured there, can be integrated with gene expression data to determine the directionality of gene expression signals and the network connection of the genes (12–14). Measuring microRNA in the serum or plasma of these three populations and integrating that data with the gene expression data to create gene networks with directionality of the gene expression signal would be a logical next step for this work.

It took 40 years from the first bronchitis conference to the sequencing of the human genome, and 15 years from the completion of the human genome to the subsetting of patients with asthma/COPD with genomic signatures in this exciting article. Although we still have a ways to go, it is clear that the pace of progress is accelerating and that integrating these gene expression data with microRNA data would be a very useful step to advance this work to the next level. ■

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