The Natural History of Asthma Phenotypes Identified by Cluster Analysis

Looking for Chutes and Ladders

Cluster analysis has greatly expanded our investigation of asthma phenotypes. These multivariate approaches explore the heterogeneity of asthma in a way hypothesis-driven univariate analyses cannot. Nearly all cluster analyses currently published, however, are cross-sectional glimpses of groups of patients as they look today without a preview of how they will look in the future (1–6). What is the natural disease progression of these new asthma phenotypes?

A good analogy is to conceptualize asthma severity as a three-dimensional labyrinth. Cross-sectional “cluster” phenotypes are different entry portals into the maze. Within the labyrinth, there are ladders that allow you to ascend to the upper level (improving asthma severity). Likewise, there are chutes that lead to the dungeon (worsening asthma severity). Many participants, however, stay on the same level, managing to sidestep the ladders and chutes (stable asthma severity). The question is whether the initial “entry” phenotype determines the journey through the labyrinth. Can a multivariate “cluster” phenotype warn of potential chutes or identify potential ladders? The article in this issue of the *Journal* by Boudier and colleagues (pp. 550–560) describes asthma phenotypes by cluster analysis at two time points 10 years apart (7). It is a glimpse into the natural history of complex asthma phenotypes and variability over time.

The most important elements in cluster analysis are the strength of the cohort and the phenotypic characteristics included in the analysis. The ideal cohort has a large number of participants with a spectrum of asthma severity (heterogeneity). Ideally, these participants would have undergone extensive clinical and biologic characterization. In general, it is difficult to have both of these ideals. Thus, current asthma cluster analyses fall into two groups, large population studies with fewer variables or smaller cohorts with extensive variables (1–6). The two approaches are complementary and each has merits as we explore asthma heterogeneity.

The cohort used in the study by Boudier and colleagues is of the former group, a combination of three very large epidemiologic populations with a limited number of variables (7). Participants with asthma were identified by self-report on the basis of answers to questionnaires, and there are inherent issues with misdiagnosis of disease, especially in cohorts that include smokers who could have other etiologies for respiratory symptoms. Only 12% of the asthma subjects in these combined cohorts had an $FEV_1 < 80\%$ predicted, suggesting that most of the participants had milder disease. Thus, the spectrum of asthma severity is narrow, and this impacts the ability of the analysis to divide subjects into distinctive clinically relevant clusters.

The seven asthma phenotypes described are most markedly distinguished by allergic sensitization as measured by skin prick testing or specific IgE levels; four of the phenotypes are atopic, and three are clearly not. Nearly all subjects in phenotypes A, D, E, and F are atopic. It is reassuring that two-thirds of these subjects remain in the same phenotypic group over the 10 years. There is some movement between phenotypes A and F; these

groups have normal lung function, and many do not have positive bronchoprovocation tests, begging the question as to whether they are primarily patients with allergic rhinitis, some of which may have airway hyperresponsiveness and asthma-like symptoms when provoked. Phenotypes D and E represent the spectrum of traditional allergic asthma with positive methacholine challenges; 25% of subjects had an $FEV_1 < 80\%$ predicted, consistent with chronic airflow obstruction and more severe disease. The movement of 38% of patients with phenotype D (more severe) to phenotype E (less severe) with only 11% worsening from E to D is inspiring to clinicians. This finding suggests that most of the patients with mild-to-moderate persistent asthma were stable or improved in the “real world” over a 10-year period.

The three nonallergic asthma phenotypes are much more difficult to interpret and not as satisfying. Many of the patients in these clusters do not have airway hyperresponsiveness to methacholine, again bringing up the possibility of a misdiagnosis of asthma. In other cluster analyses, less allergic phenotypes are most often highly symptomatic, older asthma subjects with later-onset disease, higher body mass indices, and multiple comorbidities (1, 3, 5, 8). We are not given any of these clinical characteristics for subjects in phenotypes B, C, and G, but the large odds ratios associated with adult onset asthma and phenotypes C and G suggests that these phenotypes may be similar to those described in prior cluster analyses. There is much greater movement of patients between phenotypes in the nonallergic groups; 20–45% of patients change phenotypes at the longitudinal assessment. These findings suggest that there may be a continuum of patients with nonallergic asthma rather than discrete nonallergic asthma phenotypes whose progression can be followed over time.

The study by Boudier and colleagues is a provocative look at disease progression in multivariate asthma phenotypes identified from a large cohort. It offers optimism that mild-to-moderate allergic asthma phenotypes may not progress to more severe disease phenotypes over time, implying that there are more ladders than chutes for these patients. The picture is less clear for the nonallergic phenotypes, groups that are confounded by the comorbidities common in later-onset asthma. It is important to recognize that there were very few patients with severe asthma in these combined cohorts, and thus, the temporal stability of cluster phenotypes in this subgroup of patients cannot be inferred. Severe asthma patients have the most to gain with longitudinal multivariate phenotyping approaches, since they likely have more chutes to avoid (recurrent exacerbations), and are in need of new ladders to climb (novel therapeutic approaches) (9, 10).

The next step is to perform similar longitudinal phenotypic analyses in smaller comprehensively characterized asthma cohorts that include extended physiologic measures, validated questionnaires, and biologic specimens for omics investigations. The National Heart, Lung, and Blood Institute’s Severe Asthma Research Program and the European U-BIOPRED (Unbiased Biomarkers in Prediction of Respiratory Disease Outcomes) networks are both currently performing comprehensive evaluations in longitudinal asthma protocols. Both networks are recruiting participants with milder and more severe asthma, enriching their cohorts for

the latter. As such, both networks will have a broad spectrum of asthma severity in which to investigate disease heterogeneity. These groups should extend what we know about the stability of multivariate asthma phenotypes over time and identify risk factors to predict chutes and ladders in patients with mild, moderate, and severe asthma phenotypes.

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Adiponectin: A Novel Link between Adipose Tissue and Chronic Obstructive Pulmonary Disease

Adipose tissue is an endocrine organ that produces over 50 proteins called adipokines. These act as signaling molecules and affect a wide array of bodily processes. Dysregulation of adipokines plays a crucial role in a variety of metabolic processes as obesity. Adiponectin (APN) is the most abundant adipokine and is involved in a wide variety of physiological processes, including energy metabolism, inflammation, and vascular homeostasis. The possible role of APN in inflammatory pulmonary diseases has been the subject of many recent investigations.

APN contains a carboxyl-terminal globular domain, which displays sequence homology to collagen VIII and X and to complement factor C1q and an amino-terminal collagen domain (1). APN circulates in major multimer complexes: low-molecular-weight trimers, middle-molecular-weight hexamers, and high-molecular-weight 12- to 18-mers (2). These isoforms may vary in biological potency: the high-molecular-weight isoform is the most biologically active form of APN (3). The primary effect of systemic APN on inflammation is to inhibit proinflammatory mediators (tumor necrosis factor [TNF]- α , IL-6, endothelial adhesion molecules intercellular adhesion molecule-1 and vascular cell adhesion molecule-1, and nuclear factor κ B) as well as to promote antiinflammatory mediators (IL-10 and IL-1 receptor antagonist) (4).

Mouse studies have triggered attention to the possible causative association between APN and chronic obstructive pulmonary disease (COPD). Genetically induced complete or partial deficiency of APN leads to structural changes in the lung characteristic of an emphysema-like phenotype. Proinflammatory cytokines and matrix metalloproteinases are increased in the lungs of these APN-deficient animals, and APN leads to TNF- α and matrix metalloproteinase-12 suppression (5). Consistent with the hypothesis of low or absent APN in the development of lung emphysema is the observation of endothelial dysfunction

in the lungs of adiponectin-knockout mice and the amelioration of the emphysematous phenotype by APN supplementation in these animals, suggesting that APN may play a role in lung maintenance through sustaining endothelial survival (6). These animal data suggest that hypoadiponectinemia plays a critical role in the progression of these structural lung parenchymal changes and the important role of APN in lung maintenance.

In this issue of the *Journal*, Carolan and colleagues (pp. 561–566) report that in a cohort of 633 individuals, including 432 individuals with COPD enrolled in the COPD Gene study, higher plasma adiponectin levels were independently associated with computed tomography-assessed emphysema, decreasing body mass index, female sex, older age, and lower percentage change in the pre-/post-bronchodilator FEV₁% predicted (7). The authors hypothesize a possible contribution of adiponectin in the development of emphysema. Although these cross-sectional data need further confirmation, these findings are intriguing as adiponectin-deficient mice seem protected against tobacco-induced inflammation and emphysema. Whereas exposure of wild-type mice to tobacco smoke for 6 months induced significant lung inflammation, adiponectin-deficient mice had minimal inflammation. In addition, whereas chronic tobacco smoke-exposed wild-type mice had significantly increased levels of lung mediators of inflammation, as well as significantly increased air space enlargement and decreased tissue elastance, exposure of adiponectin-deficient mice to chronic tobacco smoke resulted in no further increase in lung mediators, air space enlargement, or tissue elastance (8).

The study of Carolan and colleagues has measured systemic APN levels and has analyzed the role of this adipokine in the development of COPD phenotypes. Crucial to understanding the role of APN in relation to changes in the respiratory system will be a better knowledge of the different effects of APN in the