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Frank C Sciurba

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EDITORIAL

COPD Phenotypes: The Answers are in the Noise

While the classification of COPD into subsets of disease pathophysiology and severity has always been of interest to the medical community, never before have these issues been as important as we attempt to unravel the biochemical mechanisms and genetic variations manifesting in various subtypes of disease. Despite a common etiologic agent, tobacco smoke, the individual variation in the manifestation of disease may be quite remarkable. It is likely that variations in phenotypic presentation result from differences in basic molecular–cellular pathogenic cascades due to genetic variations in the response to environmental agents. The comprehensive discussion by Dr. Friedlander and colleagues describes the remarkable variability in patients who share the simple label of “COPD”; for example, subjects sharing similar decrements in FEV₁, the traditional metric of disease severity, may in fact vary greatly with respect to the extent and distribution of parenchymal emphysema and airway involvement (1). Additionally, the systemic pathology associated with COPD, including myopathy, malnutrition, coronary artery disease, osteoporosis and depression may vary greatly between individuals. It is likely that better characterization of these physiological, anatomical and clinical phenotypic subsets and their associations with specific pathogenic mechanisms will lead to earlier disease detection, better determination of prognosis, identification of unique therapeutic targets, and determination of short term surrogates of meaningful clinical response.

The traditional approach of basic scientists in testing a hypothesis is to introduce or alter a single condition in eugenic mice such that any variation or “noise” in the experimental response between individual animals is due to random events in the experimental environment. By contrast, variation in human response to an environmental pathogen requires a different research paradigm, as this variation is more likely related to individual differences in the biologic reaction to a given environmental or experimental condition. In fact, the statistical burden of inadequately classified cohorts with mixed disease, if not misclassification of unique entities, causes a loss of power in determining genotype-phenotype correlations, and weakens the strength of the associations when they are present (2). Thus, close attention to the “noise” in the population of COPD patients is likely to provide the answers that link the cellular and molecular biology to such variations in clinical response. It is this recognition that has empowered translational clinical scientists to become an invaluable asset to molecular scientists in designing research that has promise in effecting a meaningful impact on human disease.

Because cohorts with similar phenotypic attributes likely reflect concentrations of individuals with more similar pathophysiology, it is likely that such subclassification will identify subgroups with similar response to biologic intervention. For example, it is biologically plausible that two individuals with similar FEV₁ but differing in the magnitude of emphysema, a process characterized by loss of matrix and epithelial and endothelial apoptosis, vs. bronchiolar fibrosis, a process characterized by cellular proliferation and fibrosis may differ in response to many biologic interventions. It is thus likely that differentiation between these two entities is important if we hope to effectively target individual intervention. It is unlikely, for example, that therapy aimed at re-induction of alveolar septation or preventing matrix destruction (e.g. retinoic acid (3)), will have a beneficial impact in patients whose predominant disease is in peripheral airways. Similarly, therapy aimed at inhibiting matrix re-modeling (e.g. gamma interferon) in patients with predominant airway disease could be ineffective or even contra-indicated in those who have predominant parenchymal destruction (4). If we are to make meaningful progress in identifying effective therapy to modify disease progression in COPD, it is essential that future clinical trials include imaging and physiologic indices, not traditionally included in subject evaluation in order to better understand the subtle differences in disease manifestation.

Keywords: COPD, Emphysema, Phenotype, Diagnostic imaging, outcome assessment, genetics.

Correspondence to:
Frank C Sciurba, MD
Division of Pulmonary, Allergy and Critical Care Medicine, Department of Medicine, University of Pittsburgh School of Medicine; Suite 1211, 3471 Fifth avenue Pittsburgh, PA 15213.
email: sciurbafo@upmc.edu
classify the “noise” into unique subsets of subjects with predictably different or opposite response characteristics.

REFERENCES