Contribution of the Environment and Comorbidities to Chronic Obstructive Pulmonary Disease Phenotypes

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KEYWORDS

• Emphysema • Chronic bronchitis • Inflammation • Systemic disease

KEY POINTS

- The heterogeneity implicit to COPD suggests that a wide variety of influences including environmental and biologic factors likely contribute to an individual's disease presentation and progression.
- Certain comorbid conditions such as cardiovascular disease and osteoporosis also contribute to the heterogeneity of the patient population.
- Systemic inflammation may be pathogenically related to many of the comorbidities seen in COPD including cardiovascular disease, osteoporosis, metabolic syndrome and depression.
- New research in COPD using large patient populations with extensive clinical and biologic characterization along with advanced analytic methods will hopefully further expand our potential to identify disease phenotypes such that targeted therapies can be developed.

Chronic obstructive pulmonary disease (COPD) is a syndrome characterized by significant disease heterogeneity.[1] Whereas the presence of airflow obstruction that is not completely reversible is a hallmark of the disease, in the individual patient this obstruction may be caused by airway inflammation and remodeling, emphysema, or both. Clinicians have identified 2 basic subtypes of COPD: "pink puffers" characterized by emphysema, significant dyspnea, hyperinflation, and weight loss but with adequate oxygenation; and "blue bloaters" characterized by chronic bronchitis, hypoventilation, and obesity. It is likely that many other phenotypes exist in COPD but their relevance has not been adequately validated.[2] To provide some clarity, a recent consensus

Disclosures: C.H.M None. M.K.H Dr Han has received lecture fees from Boehringer-Ingelheim, Pfizer and GlaxoSmithKline. She has received consulting fees from Novartis, Genentech, GlaxoSmithKline, Pfizer, Boehringer-Ingelheim and Medimmune.
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Med Clin N Am 96 (2012) 713–727
doi:10.1016/j.mcna.2012.02.007 **medical.theclinics.com**
0025-7125/12/$ – see front matter

group defined COPD phenotypes as, "a single or combination of disease attributes that describe differences between individuals with COPD as they relate to clinically meaningful outcomes (symptoms, exacerbations, response to therapy, rate of disease progression, or death)."[2] The validation of phenotypes will ultimately require an iterative process (**Fig. 1**) so that groups of patients may initially be identified either by similar clinical outcome, radiologic or physiologic characteristics, biological or molecular signature, or response to therapy. Ultimately, the hope is that these patient subgroups share similar pathophysiologic processes, so that specific therapies can be developed. The goal of this article is to highlight the accumulated data regarding environmental and host factors, in particular comorbid diseases, that may help to identify and refine patient phenotypes in COPD.

ENVIRONMENT

Tobacco is the principal risk factor and environmental toxin responsible for the development of the disease in most patients with COPD. Most of what we know about the natural history of COPD is in tobacco smokers. The prevalence of COPD in smokers is approximately 20% as compared with 4% in nonsmokers.[3] This association is supported by the acceptance of the preventive effects of smoking cessation. The Lung Health Study, an interventional smoking cessation study in smokers with COPD with mild airflow obstruction, demonstrated that the decline in the rate of forced expiratory volume in 1 second (FEV_1) was greatest in patients who smoked the most and least in those who achieved sustained smoking cessation.[4] However, the fact that only one in five smokers develops COPD, points towards additional factors that contribute to its development. The importance of second-hand smoke exposure, also known as environmental tobacco smoke (ETS), should not be overlooked. Higher cumulative lifetime ETS at home and work has been associated with increased risk of COPD, even after adjustment for personal smoking history and occupational exposure.[5]

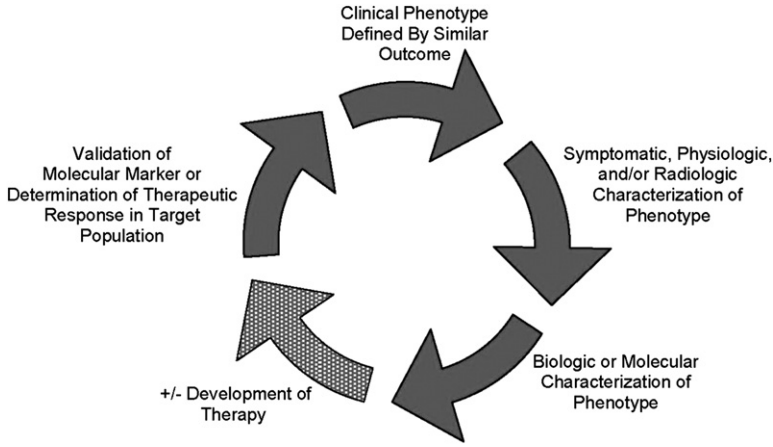

Fig. 1. Ideal phenotyping construct wherein candidate phenotypes are validated once their relevance to clinical outcomes is established. There are multiple potential points of entry into this iterative process of phenotype identification. For instance, similar clinical outcomes may define a subpopulation that leads to the identification of a biologic target and focused therapy. Alternatively, the process might begin with the differentiation of subgroups based on a biologic marker that is then validated by similar clinical response within subgroups. (*From* Han MK, Agusti A, Calverley PM, et al. Chronic obstructive pulmonary disease phenotypes: the future of COPD. Am J Respir Crit Care Med 2010;182(5):598–4; with permission.)