cells in the lungs of patients with COPD (5). The accumulation of these cells most likely represents a regenerative attempt halted by impaired RAS-to-ATII transdifferentiation capacity, eventually leading to lung regeneration failure in patients with COPD (5).

This inability to correctly regenerate is consistent with the interpretation of COPD as a structural lung disease, leading progressively to unfavorable lung mechanics and disabling symptoms largely present in older people. Noticeably, progenitor cell senescence may be a shared mechanism of different causes of COPD leading to a failed regenerative process and remodeling, and the search for senolytic drugs to treat patients with COPD has become an established field of investigation in recent years (6). Thus, we propose to also include the concept of "structural changes due to failed regeneration by the distal airways progenitor cells" into the new definition of COPD, furthering definition of the essential nature of COPD and the drive to search for new drugs. ■

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Marco Confalonieri, M.D.*
University of Trieste
Trieste, Italy

and

University Hospital of Cattinara
Trieste, Italy

Luca Braga, Ph.D.
International Centre for Genetic Engineering and Biotechnology
Trieste, Italy

Francesco Salton, M.D.
Barbara Ruaro, M.D., Ph.D.
Paola Confalonieri, M.D.
University of Trieste
Trieste, Italy

and

University Hospital of Cattinara
Trieste, Italy

ORCID ID: 0000-0002-4791-768X (M.C.).

*Corresponding author (e-mail: mconfalonieri@units.it).

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Reply to Harber and to Confalonieri *et al.*

From the Authors:

We have read with interest the comments related to the publication where we proposed that the definition and taxonomy of chronic obstructive pulmonary disease (COPD) be updated (1). Dr. Harber in his letter states that, in addition to biomass and pollution exposure, we should have acknowledged the critical role of occupations in the development and worsening of COPD. We certainly recognize the importance of certain occupations as a risk factor for airway diseases; however, the occupations most likely to cause damage work via pollution of the environment surrounding the individual. Indeed, in the study quoted by Dr. Haber to support his proposition, the insulting agent identified was fume exposure (2), an environmental pollutant of complex nature. The interest in certain unusual occupational risk factors is that they potentially identify novel mechanisms for COPD, like cadmium-induced emphysema (3), but they also are environmental pollutants.

In a separate letter, Dr. Confalonieri and colleagues offer substantial evidence that one of the pathogenetic mechanisms that may lead to COPD is that of failure to regenerate damaged lung tissue. We certainly agree with this potential mechanism and, as a matter of fact, have shown this to be a solid explanation for the clinical phenotype of patients with the emphysematous imploding phenotype (4). In their letter, Confalonieri and colleagues suggest that the updated definition of COPD should include the statement "structural changes due to failed regeneration by the distal airways progenitor cells," a topic of increasing scientific interest (5). However, as we extensively discuss in the reasoning for the reformulation of an updated taxonomy of COPD, a definition need not have the pathobiological mechanisms responsible for the structural and physiological consequences leading to the features defining the disease. As pointed out by Scadding in his classical work on disease definition (6), a disease can be defined by symptoms, by structural changes, by function, and ultimately by the causative agent. It is neither necessary nor customary for a disease definition to include the pathobiological mechanisms by which a causative agent leads to the structural or physiological abnormality. These mechanisms may change over time, as knowledge and science progress, or they may be multiple depending on the causative agent responsible for the disease. The COPD definition we proposed expands the scope of the current one; it includes symptoms, structure, physiology, and causative agents. The potential mechanism, or more likely mechanisms, responsible for COPD should be addressed in different reviews addressing that specific question. ■

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Bartolome Celli, M.D.*
Harvard Medical School
Boston, Massachusetts

Leonardo Fabbri, M.D., Ph.D.
University of Ferrara
Ferrara, Italy

On behalf of all the authors

ORCID IDs: 0000-0002-7266-8371 (B.C.); 0000-0001-8894-1689 (L.F.).

*Corresponding author (e-mail: bcelli@copdnet.org).

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Functional Criteria to Define Progressive Pulmonary Fibrosis: Searching for the Holy Grail

To the Editor:

We have reviewed with great interest the article "Validation of Proposed Criteria for Progressive Pulmonary Fibrosis" by Pugashetti and colleagues (1). The authors have assessed progressive pulmonary fibrosis (PPF) criteria proposed in different studies and their association with transplant-free survival in patients with nonidiopathic pulmonary fibrosis (non-IPF). After different analyses, the authors conclude that an FVC decline of ⩾10% and six additional PPF criteria in the absence of such decline identify patients with non-IPF interstitial lung disease (ILD) at increased risk of death or lung transplant (1).

When we assess the progression of ILD, we consider absolute or relative changes in FVC and D_{LCO} over a period of time. The absolute decrease is calculated as the initial measurement minus the final measurement, and the relative decrease is calculated as the difference between the initial and final measurements divided by the initial measurement (2). This differentiation is important. In IPF, the incidence of progression could be different using relative or absolute values (3). The use of a relative FVC decline of ⩾10% is preferred when assessing progression (4) compared with the absolute method. However, for example, the absolute 5% drop in FVC in 1 year (but not relative change) is associated with an increased risk of death and transplantation at 2 years in IPF (3).

The study by Pugashetti and colleagues (1) assessed a relative FVC decline of ⩾10%. The absolute change was not included in the study. However, they included absolute changes for other values and for D_{LCO} (1). In the discussion, they also mentioned the recently published guidelines for PPF (2). However, in these guidelines, they recommended an absolute decrease in FVC of >5% or absolute decrease in D_{LCO} (corrected for Hb) of >10% within 1 year of follow-up to define functional progression. From the data of the authors, FVC decline of ⩾10% was a better prognostic factor than those proposed by guidelines (although FVC decline >5% was not assessed, only FVC decline 5–9%). In addition, the study period extends to 4 years, in contrast with 1 year in the PPF guidelines.

From our perspective, it is important to clarify which values, methods (relative or absolute), and study periods are suitable for PPF criteria. Early identification of PPF and proper early treatment are overarching objectives. To avoid confusion in the ILD community, scientific research and guideline groups need to work together to decide which criteria are better for the early identification of PPF. ■

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María Noboa-Sevilla, M.D.
Respiratory Clinical Institute
Barcelona, Spain

Fernanda Hernández-González, M.D.
Respiratory Clinical Institute
Barcelona, Spain

and

Barcelona Research Network
Barcelona, Spain

Xavier Alsina-Restoy, R.N.
Nancy Pérez-Rodas, M.D.
Respiratory Clinical Institute
Barcelona, Spain

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