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Definition of Chronic Obstructive Pulmonary Disease: Occupational Environmental Contribution

To the Editor:

The recent proposal to reclassify chronic obstructive pulmonary disease appropriately identifies environmentally related disease (1). However, in addition to biomass and pollution exposure, the critical role of occupation in the development (2) and worsening (3) of chronic obstructive pulmonary disease should be acknowledged. ■

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Chronic Obstructive Pulmonary Disease Definition: Is It Time to Incorporate the Concept of Failure of Lung Regeneration?

To the Editor:

We applaud the proposal of Celli and colleagues (1) to provide an updated definition of chronic obstructive pulmonary disease (COPD), driven by the slow progress of therapeutic interventions to decrease morbidity and mortality. This authoritative group of experts focused on two main limitations of the previous COPD definition: *1*) the lack of identification of the disorder at its early stages in the absence of flow limitation; and *2*) the consideration of COPD as a single disease despite diverse causes other than cigarette smoking. The proposed solutions are aimed to encourage novel treatments and translational studies: *1*) incorporating into the definition objectivable early computed tomography (CT) scan changes; and *2*) describing the heterogeneity of COPD according to its recognizable causes. We noted that the revised definition of COPD addressed a clinician's typical point of view, probably with the same basic intentions of the Global Initiative for Chronic Obstructive Lung Disease guidelines. Will this be enough to describe the essential nature of COPD and particularly to stimulate more efficacious therapeutic interventions? We wish all the best for this attempt, but we argue that a change of paradigm (e.g., regenerative pathways) is desirable to drive novel therapeutic approaches. It was only in 2012 that the first demonstration of adult lung growth in humans by a multidisciplinary team of investigators focused on translational bench-to-bedside medicine (2). Now, we have abundant evidence that the lung, the organ of our body most widely exposed to the external environment, has extensive regenerative ability to respond to most injuries, rapidly regenerating damaged tissue (3, 4). COPD is characterized by both distal airways and parenchymal remodeling, which may be practically considered as due to failed regenerative processes. Recently, the highly talented interdisciplinary biomolecular investigators led by Ed Morrisey found that endothelial and mesenchymal cells in patients with COPD have different gene expression patterns from healthy individuals. In particular, they showed that the distal airway multipotent respiratory airway secretory (RAS) cells, usually able to regenerate alveoli in humans by differentiating into alveolar type II epithelial (ATII) pneumocytes cells, follow an aberrant differentiation trajectory leading to the accumulation of RAS-to-ATII transitioning

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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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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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