Is the Inflammatory Response of the Lungs in COPD Abnormal?

To the Editor:

The current definition of COPD includes the statement that “the airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking.” The term “abnormal inflammatory response” was first introduced in the definition of COPD in the 2001 GOLD (Global Initiative for Chronic Obstructive Lung Disease) article, and since then the same phrase has been used in the definition of the disease. Even in a recent article in CHEST (February 2011) by van den Berge and colleagues on small airways disease, the same term was used in the COPD definition.

This letter aims to challenge the word “abnormal” and to propose its omission from the definition of the disease in the future. New evidence related to COPD pathogenesis has emerged to support the thought that the lungs respond against cigarette smoke in a rather normal or common way of self-defending.

A cigarette contains thousands of xenobiotic compounds and free radicals that injure lung epithelium to a degree that is directly proportionate to their concentration. The first lines of lung defense are the epithelial barrier cells of the upper and lower airways and the innate immunity molecules. When toxic substances, or antigens, reach the interstitium, dendritic cells pick up the intruders and report antigenic information to the pulmonary lymph nodes, initiating an adaptive immune response.

In detail, lung epithelial barrier cells (LEBCs) line the luminal surface of the airways and are attached to neighboring cells by several structures and junctions, constituting the initial mechanical barrier in lung defense. Epithelial cells, when injured by bacterial products, viruses, oxidants, or cigarette smoke, can recruit inflammatory cells by releasing chemokines and mediators. These mediators activate alveolar macrophages and neutrophils, which in turn secrete proteolytic enzymes and, together with reactive oxygen species, damage lung tissue. Although various cellular protective mechanisms constituting an antioxidant system are in place to limit oxidative events in the cell, an imbalance of oxidants and antioxidants can impose oxidative stress upon a cell, with nucleic acid being an important target for oxidation, especially the base composition of repeated sequences, such as the microsatellite DNA.

Microsatellite DNA instability has been found in sputum cells of patients with COPD. Specifically, recent studies in patients with COPD have shown microsatellite instability exclusively in the lung epithelial cell subpopulation, supporting the hypothesis that persistent inflammation and oxidative burden in COPD could affect the cellular component of the air-lung barrier system, leading to oxidative DNA damage and consequent somatic mutations of the lung epithelia.

When altered, LEBCs emit warning signals for detection and repair of the damage. According to the “danger theory” of Matzinger, the cellular injury from any cause alerts the immune system to respond, through the release of danger signals. The adaptive immune system can recognize these products as foreign antigens and trigger an immune response. Particular in COPD, such “antigens” could be acquired from the oxidative DNA-damaged cells. At this point, the immune system reacts following the same path as in any invasion; the “danger signal” is taken up by dendritic cells and presented to the innate immune system as “non-self” danger signals, generating a cytotoxic CD8 T lymphocyte response. Such T cells are abundant in the lungs of subjects with COPD.

Similar to host immune response to a viral infection, CD8 T cells attack the altered LEBCs, performing cytotoxic functions via perforin and granzymes. The insertion of granzymes in the LEBCs activates specific apoptotic pathways, leading to cell death. Thus, it appears that the immune system reacts in a similar manner as to any intruder, by following analogous paths toward “damaged” cells even if it must turn against its own self.

To our way of thinking, all of the above is characterizing a normal rather than an abnormal inflammatory response. Humans have been fighting pathogens for millions of years and have developed quite efficient immune response in most cases. We assume that the same pathway is activated against cigarette smoking, a human habit obtained rather recently—only 500 years ago.

We propose that since we do not call the defense responses against infections abnormal, we should not call the inflammatory response in COPD abnormal. At this point, we suggest the exclusion of the term “abnormal” from the definition of COPD.

Nikolaos M. Siafakas, MD, PhD
Eleni G. Tzortzaki, MD, PhD
Crete, Greece

Affiliations: From the Department of Thoracic Medicine, Medical School, University of Crete.

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Correspondence to: Nikolaos Siafakas, MD, PhD, Department of Thoracic Medicine, Medical School, University of Crete, Panepistimiou Ave, Heraklion, 71110, Greece; e-mail: siafak@med.uoc.gr

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REFERENCES


**Response**

**To the Editor:**

We have read with great interest the comments of Drs Siafakas and Tzortzaki regarding our article on small airway disease in asthma and COPD. They suggest excluding the term “abnormal inflammatory response to cigarette smoke” from the definition currently used for COPD.

Although smoking is the most important risk factor for COPD, only approximately 20% to 30% of smokers will ultimately develop COPD. A key unanswered question is why smoking causes irreversible and progressive obstructive changes in these susceptible subjects and how they differ in their response to smoking from nonsusceptible subjects.

To clarify the abnormal response to smoking in susceptible individuals, several possible mechanisms have been put forward with respect to airway inflammation, oxidative stress, protease-antiprotease imbalance, tissue injury, and repair and remodeling. Thus far in research, patients with established COPD have been compared with control subjects without COPD. Therefore, any observed difference between these groups will as likely reflect a cause as a consequence of COPD. For this reason, it is presently unknown whether susceptible smokers exhibit a different or abnormal inflammatory response when compared with nonsusceptible smokers who will not develop COPD over time.

In this context, the findings of Silverman et al. are of interest. They demonstrated that susceptible subjects can be identified based on family history. When first-degree relatives of patients with severe early-onset COPD (defined by lung function, ie, FEV₁, <40% predicted and age <53 years) smoked, their FEV₁ was significantly lower than in subjects who smoked and were not first-degree relatives. A study is now needed that investigates if there are differences in the response to smoking between young healthy subjects who are susceptible according to the criteria of Silverman et al. and young healthy subjects who are nonsusceptible. Such a study will certainly generate highly valuable new insights in the mechanisms that contribute to COPD pathogenesis. Only then can we decide to definitively exclude the possibility that a different or abnormal response to cigarette smoking contributes to the development of COPD.

Maarten van den Berge, MD, PhD
Nick H. T. ten Hacken, MD, PhD
Judith Cohen, MD, PhD
W. Rob Douma, MD, PhD
Dirkje S. Postma, MD, PhD
Groningen, The Netherlands

**Affiliations:** From the Department of Pulmonology, University Medical Center Groningen, University of Groningen.

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**Correspondence to:** Dirkje S. Postma, MD, PhD, Department of Pulmonology, University Medical Center Groningen, Hanzeplein 1, 9713 EZ Groningen, The Netherlands; e-mail: d.s.postma@lumc.nl

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**References**

**IV Immunoglobulin Might Be Considered as a First-line Treatment of Severe Interstitial Lung Disease Associated With Polymyositis**

**To the Editor:**

We read with interest the article by Bakewell and Raghu in a recent issue of CHEST (February 2011), in which the authors relate the case of a patient with severe interstitial lung disease associated with polymyositis/dermatomyositis (ILD-PM/DM). The patient, remarkably, improved after three monthly doses of 2 g/kg IV immunoglobulin (Ig) without any other immunosuppressive agent, with sustained clinical remission after >2 years. According to the authors, IV Ig has not yet been tested as a first-line treatment of this disease. Our recent observation of a patient who did not respond to steroids and worsened after one infusion of cyclophosphamide but did improve dramatically after IV Ig is consistent with Bakewell and Raghu, who suggest that IV Ig should be considered as a potential first-line therapy for ILD-PM/DM.

Our patient was a 47-year-old man with ILD-PM/DM in the context of dyspnea associated with severe weakness. Creatine kinase value was increased to 1,110 units/L, and antinuclear auto-antibodies were positive without anti-Jo-1. The results of an electromyogram suggested a myopathy, and the results of a deltoid biopsy confirmed the diagnosis of polymyositis. Chest radiograph and CT scans revealed consolidation, with air bronchograms and ground-glass opacities in both lungs with nodular opacities. Total lung capacity (TLC) was 52% of predicted values, and vital capacity (VC) was 55%. Diffusion capacity of the lung for carbon monoxide (DLCO) was 61%. The results of BAL revealed mixed...