bilateral ground-glass opacities and thickening of the interlobular septa, whereas in some cases centrilobular nodular opacities were present. In most patients, chest radiographic findings were reported normal. The clinical significance of these findings, however, is not clear. FES is a clinical diagnosis; currently, it is not known to what extent high-cost diagnostic tests such as HRCT may improve the accuracy of the clinical examination. Although the authors suggest that HRCT in mild cases of FES may aid in diagnosis prior to development of clinical manifestations, the design of their study does not permit firm conclusions regarding the clinical value of HRCT. HRCT was performed in patients in whom a clinical diagnosis of FES had been made. This precludes any statement as far as the diagnostic role of HRCT is concerned. Furthermore, the specificity and sensitivity of HRCT is not known. At present, the existing data in the literature do not support the routine use of HRCT as a tool to diagnose the respiratory system dysfunction in FES. Further studies with appropriate designs are needed to resolve this issue. Even in the current era of high technology, FES is one of the few pathologic entities that are diagnosed based on readily available clinical criteria. Nevertheless, the study of Malagari et al may serve as a useful framework to further assess the role of HRCT in diagnosing mild cases of FES. Until the appropriate studies are available, careful clinical examination remains the “gold standard” for diagnosing FES.

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REFERENCES


COPD

Is Chemotaxis the Key?

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ver the last years, many studies were aimed at better redefining the airway inflammatory changes that are associated with COPD, the diagnostics umbrella comprising emphysema, small airways disease, and chronic bronchitis (CB). The reappraisal of inflammation of the airways as a fundamental part of the disease was possible by capitalizing, on one side, on the different tools that are available for evaluating airway inflammation from more to less invasive or noninvasive (eg, BAL or sputum) and, on the other side, on the recent progresses in immunology and leukocyte biology.

Looking back at the results of all these studies, they were somehow surprising. Neutrophils have been known for a long time as the major component of sputum in CB and COPD patients, and consistently their role in intraluminal inflammation has been confirmed, but new and important information has been added on the mechanisms of polymorphonuclear leukocyte recruitment and on their activities in the derangement of the airways and lung parenchyma. Moreover, what was really new and exciting was the observation of a role for mononuclear cell-mediated inflammation also in COPD patients. Lymphocytes and monocytes/macrophages are found in increased numbers and in the activated state in the bronchial submucosa of CB and COPD patients. It is a picture that somehow resembles that found in the bronchi of asthmatic patients, but at variance with the situation in asthma patients, in COPD patients the causative agents and the characteristics (eg, T helper-1 vs T helper-2 cytokine profile) of this reaction are still unclear. Moreover, the interaction between the mono-
nuclear and the polymorphonuclear part of airway inflammation is just starting to be addressed, with evidence of the role of chemokines and chemokine receptors.5,6

Beginning with these observations, the research focused on the possible molecular mechanisms causing airway inflammation, trying to identify the possible targets for new treatment approaches. So what is the key to airway inflammation in COPD patients? Many researchers think that neutrophil chemotaxis is the key. As a follow-up to this concept, the hypothesis that by inhibiting, or reducing, the neutrophil influx into the airways one should be able to reduce the burden of airway inflammation and, thus, to change the natural history of the disease, has arisen.

Chemotaxis is a biological phenomenon whereby a cell type migrates through barriers (eg, vessel walls or epithelial layers) and tissues toward a site of inflammation or infection. Thus, it represents a useful biological phenomenon since it allows for the allocation of resources (ie, cells and cell products) in a short time to the place where they are needed. The cells migrating to the site of chemotaxis will initiate and maintain the inflammatory processes, which may switch up self-maintaining circuits and become chronic and irreversible, causing tissue derangement and organ failure. In the case of COPD, although cigarette smoke is the cause of the disease in most patients and smoke is able to induce neutrophil chemotaxis,7,8 one of the characteristics is the continuing maintenance of the airway inflammatory picture after smoking cessation.

Chemotaxis is also a complex and multistep process in which, under a variety of stimuli, different cell types produce either the chemotactic factors or the factors that induce their production, other cells migrate through margination, deformation, and rolling adhesion mediated by adhesion molecules, and the mediators of chemotaxis and their receptors have an interplay. As an example, a long list of molecules, each of them produced by different cell types, are able to exert a chemotactic activity for neutrophils: classic chemoattractants such as C5a, leukotriene (LT) B4, platelet-activating factor, and formylmethionyl-leucyl-phenylalanine; chemokines such as interleukin (IL)-8, growth-related oncopogene (GRO)–α, GRO–β, and GRO–γ; and other recently recognized factors.9–11

In this issue of CHEST (see page 1240), Beeh and colleagues, starting from the observation that IL–8 and LTB4 are identified as neutrophil chemotactic factors in the sputa of COPD patients, demonstrate that a mouse antibody antagonist of IL–8 and an antagonist of LTB4 receptor may inhibit in vitro neutrophil chemotaxis. Similarly, an LT synthesis inhibitor has been shown to be ready for further clinical studies, and other compounds are being tested.12–14 This evidence means that if chemotaxis is the key factor in the airway inflammation of patients with COPD, there are compounds that can block it, thus opening new avenues for the treatment of this deadly disease.

Together with antichemotactic drugs, many new compounds or classes of compounds are presently in development for the treatment of COPD, such as antioxidants, protease inhibitors, adhesion molecule inhibitors, and new anti-inflammatory drugs.13,14 All of these new approaches have their rationale in cellular and molecular mechanisms of the inflammatory components in COPD that are taken as targets for the proposed treatment, but there are still a number of problems to be solved. For the antichemotactic drugs, the first problem is to identify the important mediators of chemotaxis that drive neutrophils into the airways of COPD patients. Neutrophilic chemotactic factors such as IL–8, LTB4, and GRO–α have been identified in COPD patients at different levels, in BAL,15–18 sputum,19–21 serum,22 and lung tissue.23 There is a need to clearly identify the chemotactic factors that, among many others, may be more important in COPD patients, and/or are more easily inhibited in their functional activity. As an example, Beeh and colleagues observed that the pretreatment of neutrophils with the combination of both of the antichemotactic drugs (ie, anti-IL–8 and anti-LTB4 receptor) reduced the sputum-induced chemotaxis by roughly 45%, which was less than the combined effect of either drug alone, thus suggesting the presence in the sputa of other, yet unidentified, neutrophil chemoattractants.

Chemotaxis may be quantitatively assayed in vitro using the chemotaxis chamber or chemotactic factors may be identified by immunoenzymatic methods. In both cases, methodologic problems that are caused by the presence of the natural inhibitors of some chemotactic factors25 or by the possible confounding effects of dithiothreitol on sputum sol assays26,27 may occur. In addition, it is possible that at different sites (eg, larger vs smaller airways) the "cocktail" of chemotactic factors varies. The different proportions of the various chemotactic factors that are detected would then be due to the methodology used to obtain solutes from the airways (eg, sputum, sampling more proximal airways, or BAL, sampling also the lower respiratory tract). Exacerbations of COPD, or subtypes of them (eg, bacterial), may be associated with a set of chemotactic signals that is different from that driving neutrophilic inflammation during the stable state, a difference that can be hypothesized also for the other COPD patient groups such as current smokers vs former or never-smokers.17,28,29 Severe and mild-to-moderate stages
of the disease are associated with different cellular inflammatory bronchial infiltrates and also may be characterized by distinct sets of chemotactic factors. The genetic background of patients is probably important, as the same agent (e.g., cigarette smoke) could cause different molecular responses in patient subpopulations sharing particular alleles for one or more chemotactic factors.

After identifying and antagonizing the relevant neutrophil chemotactic factors, and certainly IL-8 and LTB4 are good candidates, one should ask to what extent the airway inflammation in COPD patients would be reduced. Together with variable bronchospasm and hyperreactivity, the features of COPD causing airflow limitation comprise a substantial reduction in the caliber and number of small airways, the loss of alveolar attachments causing air trapping, exaggerated mucus production, and the presence of airway inflammatory infiltrates. Neutrophils and their products contribute to all these features, but other cell types (e.g., macrophages, lymphocytes, or eosinophils) are surely also involved in the genesis of airway inflammation. At least some activities of neutrophils in COPD could be surrogated by other cell types, such as macrophages. Thus, the suppression only of the neutrophil-dependent part of inflammation, even if possible, may not be sufficient to cure COPD while it could have also serious side effects on bacterial infection susceptibility.

Since one of the targets of the antichemotactic strategies seems to be IL-8 or its receptor, it should be remembered that the chemokine system is redundant, with many molecules sharing overlapping effects and acting through the same surface receptors, and it may be difficult to inhibit in vivo chemotaxis significantly by blocking just one chemokine or receptor. Lastly, it has been demonstrated that similar activities claimed for the new antichemotactic drugs are exerted, directly or indirectly, by old drugs that are used worldwide, such as theophylline.

In conclusion, the antichemotaxis approach is probably not ready for prime time in the treatment of COPD. Despite all of the above-mentioned limitations, it represents a very good working hypothesis, introducing for the first time the concept of an etiologic treatment that would counteract the noxious effects of the neutrophilic inflammatory burden in the airways of COPD patients. The best reward for the hard work of many research groups will be in unveiling the molecular pathways of COPD airway inflammation.

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A Model of Human Lung Cancer

Over the last several decades, progress in the treatment of bronchogenic lung cancer has been disappointing. Lung cancer remains the number one cancer killer in the United States. Lung cancer kills more US citizens than colon cancer, breast cancer, and prostate cancer combined. Although most cases of lung cancer could be prevented, the treatment of lung cancer is often disappointing.

New modalities, new drugs, and new methods with which to test the utility of new approaches are needed. In the study of infection, laboratory and animal models have proven invaluable. In the study of human cancer, the efficacy of new treatment ideas in various cell lines can be investigated. This provides preliminary useful information, but it does not provide information on the effectiveness of the agent or agents in the prevention of death or metastasis. Such methods also do not provide us with data about toxicity or tissue penetration. These issues can be studied in human subjects, but such studies are expensive, time consuming, and of potential risk to subjects. An animal model of human lung cancer may accelerate the investigation of new treatment ideas. This approach allows a new agent or idea to be used alone or in combination with various other agents, in rapid succession and in a relatively inexpensive manner.

In this issue of CHEST (see page 1248), Tanaka et al use severe combined immunodeficiency (SCID) mice to develop an animal model of human pulmonary metastatic lung cancer. Non-small cell lung cancer cells (EBC-1) were injected into the flank of SCID mice. The animals soon developed metastatic pulmonary nodules. The tumor used is a human bronchogenic epidermoid carcinoma. It produces neutrophil elastase. Staining for neutrophil elastase confirmed that the metastatic nodules were the same tumor as the tumor implanted in the animals flank. These pulmonary metastatic nodules were evident by week 7. Surgical removal of the flank tumor at week 3 or at week 5 did not prevent the formation of metastatic pulmonary nodules in any of the mice. Blood samples obtained 3 weeks after implantation revealed human β-actin messenger RNA. This confirmed the presence of metastasis as early as 3 weeks and explained the failure of surgical removal in the prevention of the spread of the human lung cancer.

With this model, it would be possible to investigate the role of traditional chemotherapeutic agents in various combinations in the hopes of finding the best approach to traditional treatment of nonresectable lung cancer. It also gives us a model to investigate neoadjuvant drugs, as well as a method to investigate new ideas in the treatment of lung cancer. Indeed, Inada et al² have already used this model to investigate a neutrophil elastase inhibitor in the treatment of this same cancer cell line (EBC-1). Other human bronchogenic carcinoma cell lines, or any other malignant cell line, could be investigated using this SCID model.