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Pulmonary Alveolar Proteinosis — Is Host Defense Awry?

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Pulmonary alveolar proteinosis is a rare disorder caused by abundant accumulation of surfactant-derived components in the lungs. The incidence is estimated to be 0.36 case per million population, and the prevalence, 3.70 cases per million.¹ About 500 cases have been recorded in the literature.

The condition usually presents as progressive dyspnea and a minimally productive cough. There are elevated serum levels of products derived from pulmonary epithelial cells, including cytokeratin 19, the mucin KL-6, and surfactant proteins A, B, and D. Pulmonary-function testing reveals a restrictive pattern and a disproportionate reduction in diffusing capacity. Patients often have hypoxemia, and the partial pressure of oxygen in the arteries is elevated as compared with that in the alveoli. The appearance of the lungs on high-resolution computed tomography is often a homogeneous ground-glass haze overlaid by thickened interlobular septa forming geometric shapes — the “crazy paving” pattern.

Diagnosis usually requires lung biopsy. The characteristic pathological feature is the filling of alveoli and distal bronchioles with surfactant-derived material that is granular, acidophilic, acellular, and amorphous; periodic acid-Schiff staining is positive and diastase-resistant. The material consists of approximately 90% lipid (primarily phospholipids), 10%

protein, and 1% carbohydrate and is usually sterile. Large foamy alveolar macrophages are present, and the alveolar structure is preserved until late in the course of disease. Mild interstitial lymphocytic infiltrates may be present.

Pulmonary alveolar proteinosis results either from decreased degradation of surfactant or from surfactant dysfunction and is classified as primary, secondary, or congenital. The congenital type has been attributed to one of two rare mutations: one causes a deficiency of surfactant protein B, and the other causes abnormalities in the β chain of the receptor for granulocyte-macrophage colony-stimulating factor (GM-CSF). Secondary pulmonary alveolar proteinosis occurs in patients with systemic inflammatory diseases or cancers (most commonly hematologic) or in association with inhalational exposure to silica, aluminum dust, titanium dioxide, or other material.

Primary pulmonary alveolar proteinosis accounts for nearly 90% of cases and is virtually always attributable to neutralizing GM-CSF autoantibodies, which prevent the binding of GM-CSF to GM-CSF receptors on alveolar macrophages (see diagram). GM-CSF-initiated signaling plays a unique, nonredundant role in alveolar macrophage function and pulmonary homeostasis.

The hypothesis that pulmonary alveolar proteinosis is due to ineffective signaling by GM-CSF re-

ceptors was first put forward in 1994, when Stanley et al.² and Dranoff et al.³ simultaneously reported on mice in which both alleles of the gene for GM-CSF are disabled. These GM-CSF^{-/-} mice have striking pulmonary pathologic characteristics that closely resemble those of patients with pulmonary alveolar proteinosis, suggesting that the intracellular signaling initiated by the binding of GM-CSF to its receptor is critical to pulmonary surfactant homeostasis. Signaling initiated by GM-CSF receptors is mediated through PU.1, a transcription factor modulating the expression of many genes that are important in the terminal differentiation of alveolar macrophages. Functions regulated by PU.1 include surfactant degradation, expression of pathogen pattern-recognition receptors, toll-like-receptor signaling, phagocytosis, and bacterial killing. Reconstitution of PU.1 in GM-CSF-deficient alveolar macrophages restores most of these functions. GM-CSF signaling also enhances the function of peroxisome-proliferator-activated receptor γ (PPAR γ), another transcription factor that regulates many cellular functions, including intracellular lipid metabolism. These findings explain how inhibiting the binding of GM-CSF to its receptor causes decreased clearance of surfactant from the alveolar spaces. GM-CSF is required for the terminal differentiation and function of alveolar macrophages

Pathophysiology of Pulmonary Alveolar Proteinosis.

GM-CSF-initiated signaling (Panel A) plays unique, nonredundant roles in alveolar macrophage function and pulmonary homeostasis, including terminal differentiation and survival of macrophages, intracellular lipid metabolism, surfactant catabolism and recycling, expression of pathogen receptors, and phagocytosis and killing. These functions are inhibited when neutralizing GM-CSF autoantibodies bind to GM-CSF (Panel B), block its binding to the α chain of the GM-CSF receptor, and prevent assembly of the GM-CSF-receptor complex. Thus, inhibition of GM-CSF binding to its receptor by autoantibodies results in decreased clearance of surfactant from the alveolar spaces, the hallmark of pulmonary alveolar proteinosis.

but not for those of other tissue macrophages — which may explain why pulmonary alveolar proteinosis is primarily a lung disease.⁴

The discovery that nearly all patients with primary pulmonary alveolar proteinosis have high titers of GM-CSF antibodies has led to the development of new therapies based on granulocyte colony-stimulating factor (G-CSF) supplementation. Previously, therapy consisted of whole-lung lavage, which results in numerous complications and does not address the pathogenetic mecha-

nisms. Administration of exogenous GM-CSF appears to help many patients, and its potential as a subcutaneous or aerosolized therapy is being evaluated.

Whether patients with pulmonary alveolar proteinosis have defects in host defense and innate immunity is not clear, nor is the effect of such defects. GM-CSF^{-/-} mice clearly have a defect in pulmonary defense against pathogens, as well as extrapulmonary abnormalities and a decreased susceptibility to experimentally induced autoimmune disorders. Patients with pulmonary alveo-

lar proteinosis do not have deficient expression of GM-CSF, but they have neutralizing GM-CSF autoantibodies, which may account for differences between host defense defects in such patients and defects in mice. Although secondary infections have been described in these patients, our understanding of host defense in this disorder is limited by its rarity, the variability of its outcomes, and reporting biases. Patients may be at risk for secondary infections, but bacteria that commonly cause respiratory infections are not often the inciting

agents.¹ Opportunistic pathogens — most commonly nocardia, but occasionally cryptococcus, histoplasma, aspergillus, or *Mycobacterium tuberculosis* — have been reported in about 13% of patients,¹ with systemic infection documented in some cases. In a review of 65 cases in which death was attributable to pulmonary alveolar proteinosis, respiratory failure was the apparent cause of death in 47 cases (72%), whereas uncontrolled infection was the cause in 12 (18%).¹ These findings suggest that clinically important lung infections occur in some patients and that systemic infections are less common.

Few researchers have investigated whether GM-CSF autoantibodies cause defects in cells, other than alveolar macrophages, that express GM-CSF receptors. In this issue of the *Journal*, Uchida et al. report on the effects of GM-CSF autoantibodies on neutrophil functions (pages 567–579). Their observations show that neutrophils from patients with pulmonary alveolar proteinosis have defects in both basal and GM-CSF–primed antimicrobial functions. In particular, the phagocytic index and phagocytic capacity of neutrophils isolated from these patients were approximately 90% and 30% lower, respectively, than those of neutrophils from healthy control subjects. The basal capacity for adhesion to plastic, the oxidative burst in whole blood, and the killing of *Staphylococcus aureus* were also reduced. Furthermore, GM-CSF priming in vitro was impaired. Similar defects in basal neutrophil functions were observed in GM-CSF^{−/−} mice, al-

though no defect in GM-CSF priming was observed. The defect in affected human neutrophils was mimicked by treating blood from healthy control subjects with GM-CSF autoantibodies. Thus, neutrophils from patients with pulmonary alveolar proteinosis have functional defects when tested in vitro.

How the signaling of GM-CSF through its receptor on neutrophils augments neutrophil function remains an important question.⁵ PU.1 is apparently critical in GM-CSF–initiated signaling in alveolar macrophages but not in neutrophils, since Uchida et al. show that neutrophils from patients with pulmonary alveolar proteinosis do not have lower PU.1 expression than those from healthy control subjects. Furthermore, defects in neutrophil function are apparent in vitro, but it is not clear how they contribute to a defect in host defense in vivo. Humans and mutant mice with defects in innate immunity, including abnormal neutrophil function, often have increased blood levels of neutrophils, G-CSF, and cytokines; the failure to destroy pathogens leads to the persistence of pathogen-induced stimuli. In contrast, in the study by Uchida et al., patients with pulmonary alveolar proteinosis who had defective neutrophil function in vitro did not have increased neutrophil counts and serum G-CSF levels, suggesting that their host defense and innate immunity were sufficient for managing daily exposures to common pathogens and commensal organisms. Clinically apparent infections, especially with opportu-

istic microbes, do occur in some patients; microbes were identified at presentation in more than half the patients studied by Uchida et al.

Whether host defense mechanisms are able to compensate for defects in neutrophil and macrophage function until the environment delivers a particular pathogen or a large load of pathogens, or until a combined assault is made on the immune system, remains to be elucidated. The absence of repeated infections, particularly in the lungs, is surprising, given the magnitude of the neutrophil defects seen in vitro; perhaps products of surfactant degradation have important antimicrobial effects. Clearly, the study by Uchida et al. raises important, provocative questions that beg to be pursued.

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