Alveolar proteinosis: a disease of mice and men

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PULMONARY ALVEOLAR PROTEINOSIS (PAP) is a rare but potentially deadly disease characterized by an accumulation of surfactant in the alveolar air spaces, which ultimately results in impaired gas exchange (5). Although a few cases of this disease can be attributed to exposure to dusts such as silica, the etiology of most cases is not known.

Insights, some quite surprising, into the possible mechanism of accumulation of surfactant in PAP have come from a variety of mouse models. The first clue in the mystery was provided by the granulocyte-macrophage colony-stimulating factor (GM-CSF) knockout mouse (3, 12). Initially characterized as a factor from lung-conditioned medium that stimulated the proliferation and differentiation of immune cells from hematopoietic progenitors, GM-CSF has been identified as a 23-kDa glycoprotein that also modulates the function of mature hematopoietic cells. Thus it seemed logical to speculate that depletion of GM-CSF would affect hematopoiesis. However, the GM-CSF-deficient mice had a normal number of peripheral blood cells, bone marrow progenitors, and populations of tissue hematopoietic cells. Unexpectedly, the mice all exhibited excessive intra-alveolar accumulation of surfactant lipids and proteins in the air spaces. Additional evidence for involvement of this cytokine in the development of PAP in mice was provided by further studies (9, 10) in which depletion of GM-CSF from small uncontrolled clinical studies. Furthermore, unfolding evidence demonstrates that the scenario is not as simple as the mouse models would lead one to believe. This is not surprising because PAP is likely a common phenotypic response of the lung to a number of biochemical or molecular abnormalities. In some patients, defective expression of GM-CSF/interleukin (IL)-3/IL-5 receptor common (IL)-3/IL-5 receptor common β-chain has been identified (1). Defective hematopoietic response to exogenous administration of GM-CSF in PAP patients also suggests that an abnormal GM-CSF receptor could be pathogenic in the disease in some cases (7, 11). It has also been demonstrated that some patients with PAP have anti-GM-CSF antibodies, which may neutralize its activity (6, 13). However, the direct relevance of antibodies to GM-CSF in the pathogenesis of the disease has yet to be demonstrated. For example, some patients with PAP have measurable levels of free GM-CSF in both lavage fluid and serum (2). Furthermore, as Kitamura et al. (6) pointed out, antibody to GM-CSF is found commonly in IgG preparations and in patients receiving GM-CSF therapeutically, yet there are no reports of PAP in these patients. It is also possible that only small amounts of GM-CSF are required for bioactivity because, like other cytokines, GM-CSF receptor...
density is very low (100–300 receptors/cell), and cytokine activation of intracellular effects through receptor binding requires only 5–10% receptor occupancy. Other authors (14) have shown that elevation of IL-10 in some patients with PAP may contribute to reduced GM-CSF levels. In any case, treatment with exogenous GM-CSF would not be expected to be an effective treatment for PAP in the scenario where antibodies are present or receptors are defective.

Although the paper by Yoshida et al. (15) provides important new information about the mechanism by which a deficiency of GM-CSF induces alterations in surfactant metabolism, many unanswered questions remain about this complex disease. Additional studies with both mice and humans that lead to a further understanding of macrophage-degradative pathways of surfactant and how these pathways might be upregulated as well as to an understanding of how GM-CSF affects macrophage differentiation could provide important clues about the etiology and treatment of PAP.

REFERENCES