Mice carrying a null allele of the CM-CSF gene develop progressive accumulations of surfactant lipids and proteins in the alveolar space, the defining characteristic of pulmonary alveolar proteinosis (PAP) (1). Despite the fact that GM-CSF promotes proliferation and differentiation of hematopoietic progenitors of neutrophils and macrophages, these animals have normal steady state hematopoiesis, but also manifest lymphoid hyperplasia in the airways (1), and a high incidence of pneumonia (2). The gene-targeting experiments described by Huffman and co-workers (3) involve a double mutant form of mice overexpressing GM-CSF specifically in the respiratory epithelium. These mice lack all stigmata of PAP; however, marked alveolar infiltration with macrophages was noted. Remarkably, neither the absence nor the excess of GM-CSF has any detectable influence on the expression of mRNAs of the surfactant proteins, SP-A, SP-B, and SP-C. In contrast, the amount of alveolar SP-A, SP-B, and disaturated phosphatidylcholine were an order of magnitude higher in the GM-CSF $^{-/-}$ mice than in those expressing GM-CSF. These results suggest that PAP caused by the absence of GM-CSF is due to a deficiency of clearance and/or catabolism of the components of surfactant.

Type II cells and alveolar macrophages are the major sites of surfactant phospholipid clearance and catabolism. Surfactant components taken up by the type II alveolar cells may be either degraded within lysosomes to precursor molecules or processed to multivesicular bodies before secretion as lamellar bodies in the recycling pathways. In healthy adult animals the intraalveolar ($t_{1/2} < 4$ h) and intrapulmonary ($t_{1/2} < 8$ h) turnover rates of surfactant phospholipids are rapid and unsaturable when a 10-fold excess of exogenous surfactant is added to the alveolar compartment (4). According to labeling experiments, the pulmonary $t_{1/2}$ for saturated phosphatidylcholine and SP-A were dramatically increased in GM-CSF $^{-/-}$ mice (5). However, despite the slow turnover rate the alveolar material was surface active.

According to Huffman et al., SP-C linked overexpression of GM-CSF increased the number of alveolar macrophages (3). However, in PAP due to the absence of GM-CSF, alveolar macrophages are present, although enlarged and laden with lipids and surfactant proteins. This finding is consistent with the role of GM-CSF in inducing differentiated functions in inflammatory cells (incidentally these include activation of phospholipases, proteases, and other proteolytic enzymes) and supports the hypothesis that PAP is associated with a deficient surfactant catabolism by alveolar macrophages. Of interest was the finding of marked alveolar infiltration with macrophages in GM$^{+/-}$, SP-C-GM^{+} mice suggestive of inflammatory cell chemotaxis or chemokinesis by GM-CSF. Other possible targets include type II cells, Clara cells, and cellular receptors for surfactant components (particularly collectin receptors or specific receptors for SP-A). In the future these knock-out models may be useful in studies defining the cellular localization and specific structures or activities limiting the rate of surfactant metabolism.

PAP is a heterogenous group of congenital and acquired diseases characterized by accumulation of large quantities of lipid- and protein-rich eosinophilic material within the alveoli and airways. A fatal form of congenital PAP results from a mutation in a 2-basepair insertion (121ins2) resulting in a reading frame shift and introduction of a premature translation stop codon with SP-B mRNA instability. Surfactant from these infants lacks SP-B (6, 7) and is associated with abnormally high quantities of surfactant phospholipids (except phosphatidylglycerol), SP-A, and an immature proto-SP-C in alveolar fluids obtained by tracheal aspiration or lung tissue. SP-B deficiency is additionally characterized by disruption of both type II cell morphology and cell polarity. Surfactant replacement therapy in these infants has been ineffective. Furthermore, in infants undergoing lung transplantation and after exogenous bovine surfactant therapy, anti–SP-B antibodies have developed with subsequent lung dysfunction. A genetic defect in the epithelial transport of cationic amino acids is also associated with increased incidence of fatal PAP in the adult. Although the eliciting element in the case of adult PAP is unknown in most cases, in animal models and human disease PAP appears to represent a reaction to a particular form of lung injury (8). A number of toxic insults to the lung (silica exposure, NO_2, ozone, and $ONOO^{-}$) may result in alveolar proteinosis (8). Exposure to silica increases surfactant pools several fold. Type II cells from silica-exposed rats increase in size and number containing increased total quantities of phospholipid and SP-A and have increased activities of several enzymes involved in phospholipid synthesis. In contrast, cationic amphiphilic drugs result in alveolar phospholipidosis. The absence of GM-CSF or its receptor as one cause of human PAP remains to be evaluated, and the role of GM-CSF in congenital SP-B deficiency requires study.

Inflammatory cells in airways and airspaces have an important defense function against bacteria and viruses. Dysregulation of inflammatory cell activity could result in lung injury. A perturbation caused by either lack of or overexpression of GM-CSF may have detrimental effects on host defense. The activity of GM-CSF is developmentally regulated (9). During the fetal period the pool size of surfactant (per respiratory surface or per gram body weight) may exceed those in the adult by a factor of 10 and be controlled by the de novo synthesis and the slow rate of catabolism (4). PAP-like conditions may be part of the transient developmental phenomena or a reaction to lung injury that disturbs surfactant recycling. The roles of GM-CSF and other cytokines in alveolar homeostasis during non-steady physiological and pathophysiological states remains to be elucidated.

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