Shared Mechanisms of Lung Injury and Subsequent Fibrosis: Role of Surfactant Proteins in the Pathogenesis of Interstitial Pneumonia in Hermansky-Pudlak Syndrome

Key words: surfactant, epithelial cell, Hermansky-Pudlak syndrome, interstitial pneumonia, pulmonary fibrosis

The pathogenesis of interstitial pneumonia is not well recognized, although numerous investigations have been reported. Hermansky-Pudlak Syndrome (HPS) is characterized by hypopigmentation, prolonged bleeding times and accumulation of ceroid-like materials in alveolar macrophages (1), and is extremely rare in Japan. It is sometimes combined with interstitial pneumonia, which is radiographically and pathologically similar to the typical usual interstitial pneumonia (UIP). HPS with interstitial pneumonia is primarily associated with HPS1 gene abnormality, located in chromosome 10q23.1–q23.3 (2). Kobashi et al reported typical features of the clinical manifestations in an HPS patient with interstitial pneumonia without mutation of HPS1 gene (3). A case with a normal HPS1 gene progressing to interstitial pneumonia associated with HPS is very intriguing.

The pathological features of interstitial pneumonia associated with HPS demonstrated alveolar septa displaying florid proliferation of type-II pneumocytes, patchy fibrosis with lymphocytic and histiocytic infiltration around honeycombing (4). Type-II pneumocytes are peculiarly enlarged by the accumulation phospholipids. The ultrastructure of type-II cells showed a large number of giant lamellar bodies that compressed the nucleus with occasional cytoplasmic disruption. These findings indicate formation of cellular degeneration with an over-accumulation of surfactant, the so-called “giant lamellar body degeneration” (Fig. 1). This is a basic defect in the formation and secretion process of surfactant by type-II cells in HPS, which induces type-II cell death leading to the progression of HPS-associated interstitial pneumonia. In general, pulmonary surfactant is required for adaptation to air breathing after birth; it reduces surface tension at the air-liquid interface in the alveolus to maintain lung volumes during the respiratory cycle (5). Surfactant deficiency induces respiratory distress in infants. Surfactant lipids consist of predominantly phosphatidylcholine, and the surfactant protein B (SP-B) and C (SP-C) are co-transported to lamellar bodies, which is a major intracellular storage organella of pulmonary surfactant. Lamellar bodies are secreted into the air space in response to stretch, β-adrenergic and purinergic stimulants. After exocytosis, lamellar bodies unravel and undergo a dramatic change in ultrastructural morphology, producing tubular myelin that represents the major extracellular pool of surfactant lipids from which mono- and multi-layered films are formed. Intracellular and extracellular surfactant pool sizes are precisely maintained by the regulation of synthesis, secretion, reuptake, reutilization and catabolism.

Hereditary SP-B deficiency in humans exhibits severe respiratory distress after birth. The pathological features in these infants are often characterized as infantile desquamative interstitial pneumonia (DIP) or congenital pulmonary proteinosis (6). In the fibrotic disorders, transforming growth factor-β (TGF-β) is known as an inhibitor of tran-

Figure 1. Pathological features of giant lamellar body degeneration examined by electron microscopy. Peculiarly enlarged lamellar bodies are seen in type-II pneumocytes (This photo was donated by Y. Nakatani at Chiba Univ.) Bar=5 μm.
scription of SP-B gene (SFTPB) (7). So we recognize that TGF-β-induced fibrogenesis in aged people may accelerate the collapse of the alveolar space by the inhibition of SFTPB, which further promotes type-II cell death and pulmonary fibrosis.

Mutation of SP-C gene (SFTPC) also causes acute and chronic pulmonary disease in humans. Chronic lung disease caused by SFTPC mutations manifests at various ages from childhood to adulthood. In the case of the familial form of pulmonary fibrosis (FPF), SFTPC mutations were reported as a critical factor for development of interstitial pneumonia (8). The pathological features of SP-C deficiency also show numerous abnormal lamellar bodies detected by electron microscopic analysis. Interestingly, the SFTPC mutation shares at least two different pathological features of interstitial pneumonia such as desquamative interstitial pneumonia and nonspecific interstitial pneumonia.

These diseases characterized by SFTPC mutation may represent pleiotropic manifestations of the same central pathogenesis. In contrast, there are undistinguishable pathological features of pulmonary fibrosis, which could be induced by different gene mutations, i.e. the presence or absence of HPS1 gene mutation (3).

Deficiency and/or dysfunction of any kind of molecules affecting intracellular transport and maturation of surfactant proteins may presently induce type II cell death, and subsequent proliferation of fibroblast.

Considering a shared mechanism of lung injury, the molecules affecting the life cycle of surfactant proteins will be research targets even in aged-onset lung injury and in subsequent emphysema and fibrosis.

References