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Hermansky-Pudlak Syndrome Interstitial Pneumonia It's the Epithelium, Stupid!

Hermansky-Pudlak syndrome (HPS) is a rare inherited disease primarily affecting the intracellular biogenesis of lysosome-related organelles (1). The clinical spectrum of this disease includes oculocutaneous albinism, a bleeding diathesis, colitis, and lung fibrosis resembling idiopathic pulmonary fibrosis (IPF) in some. HPS interstitial pneumonia (HPSIP) shares the same aggressive course of lung fibrosis with IPF, resulting in progressive dyspnea, reduced exercise capacity, loss of life quality, and eventual death or need for lung transplantation (2, 3). HPSIP also shares the usual interstitial pneumonia histopathology with IPF, but, in contrast, it is characterized by giant lamellar body formation in alveolar epithelial cells type II (AECII), resulting in AECII swelling (2). Of note, lung fibrosis has only been observed in HPS-1, HPS-4 (4, 5), and HPS-2 (6) subtypes, which are associated with defects in the Biogenesis of Lysosome-Related Organelles Complex-3 or the Adaptor Protein-3 Complex. Interestingly, although HPS mono-mutant mice do not spontaneously develop lung fibrosis, HPS-1 and HPS-2 mice are highly susceptible to bleomycin-induced lung fibrosis (7), and mice with a combined HPS1 and HPS2 defect develop spontaneous pulmonary fibrosis (8, 9).

AECII are highly active cells, as they secrete pulmonary surfactant, which is stored in lamellar bodies. Lamellar bodies are lysosome-related organelles in AECII. Thus, it is not surprising that murine and human HPSIP are associated with defective surfactant processing and transport, causing lysosomal and endoplasmic reticulum stress in AECII (8, 10).

It is also known that alveolar macrophages are activated in patients with HPS-1 (11), HPS-1 and HPS-2 mono-mutant mice (12), and HPS1/2 double-mutant mice (13). In addition, the enhanced cytokine secretion by alveolar macrophages of patients with HPS-1 is down-regulated by pirfenidone (11). These data suggest a putative role for alveolar macrophages in driving lung fibrosis in patients with HPS-1.

Despite these findings, evidence indicating a prominent role of AECII in the pathogenesis of HPSIP is mounting. It is reported that lung fibrosis in several mono- and double-mutant mice only occurred in mice with extensive AECII apoptosis (7, 8). Likewise, an association between the dysregulation of AECII and macrophage activation via S-nitrosylated surfactant protein D demonstrates that a secretory product of AECII can contribute to lung inflammation in HPSIP (14).

In this issue of the *Journal*, Young and colleagues (pp. 1014–1024) add further experimental evidence to the conceptual view

that the alveolar epithelium is centrally involved in the development of HPSIP (15). For this work, the authors focused on HPS-1 and HPS-2 murine models. Although they do not develop spontaneous pulmonary fibrosis, these murine models are highly susceptible to bleomycin-induced pulmonary fibrosis and, thus, are models for human HPS pulmonary fibrosis. Young and coworkers generated bone marrow chimeric mice and report that, in spite of transplanting HPS-1 and HPS-2 mutant mice with healthy wild-type bone marrow cells, these mice continued to develop a similarly severe lung fibrosis in response to bleomycin challenge. Furthermore, wild-type mice receiving bone marrow cells from HPS-1 or HPS-2 mutant mice did not show impressive fibrotic changes. However, epithelial-specific correction of the HPS2 defect largely prevented development of bleomycin-induced lung fibrosis, normalized cytokine concentrations, and corrected AECII lamellar body size. These observations are highly important as they show that AECII have a central role in the pathogenesis of HPSIP, and this publication adds to the growing body of literature that demonstrates the significant contribution of the alveolar epithelium to the initiation and development of pulmonary fibrosis.

Another important event in HPS lung fibrosis addressed by Young and colleagues is AECII apoptosis, a persistent finding in human HPSIP, HPS1/2 double-mutant mice developing lung fibrosis (8), and other forms of fibrotic lung disease (16). Young and colleagues report early AECII apoptosis in HPS-2 mice in response to bleomycin challenge. When treated with a pan-caspase inhibitor, these mice displayed decreased lung fibrosis and AECII apoptosis, which provides additional proof that epithelial apoptosis has a central role in HPSIP. Although no evidence of endoplasmic reticulum stress was found, the observed AECII apoptosis may be a result of lysosomal stress, which was not analyzed in this study.

The study by Young and colleagues strengthens the pathomechanistic concept that, like in familial and sporadic IPF, dysfunction of AECII underlies the development of lung fibrosis in HPS (16–18). The comprehensive and provocative data presented in this publication raise several additional questions and open the door for novel therapeutic concepts. For example, would transgenic correction of the HPS1 epithelial defect in HPS-1 mice be associated with findings similar to those presented in this publication? Is correction of lamellar body morphology in these HPS-2 mice associated with normalization of defective surfactant

secretion? Would transgenic correction of the HPS-2 epithelial defect in HPS1/2 double-mutant mice prevent the development of spontaneous pulmonary fibrosis? Is epithelial-specific correction of the underlying genetic defect or inhibition of AECII apoptosis a potential therapy for HPS pulmonary fibrosis? Further research is indicated to answer these questions and improve the understanding of HPS pulmonary fibrosis and fibrotic lung disease in general.

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CD14⁺S100A9⁺ Myeloid-derived Suppressor Cells Portend Decreased Survival in Patients with Advanced Lung Cancer

It has been clearly shown from multiple preclinical studies that myeloid-derived suppressor cells (MDSC) serve as a target for inhibiting tumor growth (1–3). Although studies in humans have shown the presence of MDSC in different pathological conditions, understanding their clinical significance in cancer requires the full characterization of these cells. The characteristics of MDSC have been described for several human malignancies, including melanoma, colon cancer, and renal cell carcinoma, but the identification of a unique set of markers for human MDSC has

been challenging because MDSC gene expression varies in different tumor types.

Feng and colleagues in this issue of the *Journal* (pp. 1025–1036) describe the characteristics of the CD11b⁺CD14⁺S100A9⁺ monocytic MDSC and their clinical relevance in patients with advanced non-small cell lung cancer (NSCLC) (4). The identification of markers for the characterization of MDSC in lung cancer is useful because only limited data are available on specific markers. The authors evaluated the characteristics of MDSC in the peripheral