Function and Pathophysiology of ABCA3

○Nobuya Inagaki[1,2], Yoshihiro Matsumura[2], and Nobuhiro Ban[2]
([1]Grad. Sch. of Med., Kyoto Univ. and [2]Akita Univ. Sch. of Med.)

Pulmonary surfactant is a complex mixture of lipids and proteins that reduces surface tension at the air-liquid interface thereby preventing end-expiratory collapse of the alveoli of the lung. We reported earlier that ABCA3, a member of the ATP-binding cassette (ABC) transporter superfamily, is expressed exclusively in alveolar type II cells and is localized mostly at the limiting membrane of the lamellar bodies in human lung. We also found that ABCA3 protein expression is dramatically increased just before birth and is upregulated by glucocorticoids. Therefore, we proposed that ABCA3 functions as a transmembrane transporter of lipid components of pulmonary surfactant. Recently, various mutations in the *ABCA3* gene have been reported in full-term newborns with respiratory distress syndrome, indicating an important role of *ABCA3* in human lung disease.

In the present study, to determine the pathophysiological role of these mutations in fatal surfactant deficiency, we characterized the subcellular localization, glycosylation, and ATP-binding and ATP-hydrolysis activities of GFP-tagged wild-type and the ABCA3 mutants so far identified in fatal surfactant deficiency patients, expressed in cultured cells. Analyses of the ABCA3 mutants permit classification of fatal surfactant deficiency due to ABCA3 mutation into two categories. Furthermore, to investigate the function of ABCA3 and its role in pulmonary surfactant biogenesis, we generated *Abca3*-deficient mice by homologous recombination and narrowed down the candidate substrates of ABCA3 protein by thin-layer chromatography (TLC) and electrospray ionization mass spectrometry (ESI/MS) analysis of lipids extracted from *Abca3*-deficient lung.