S07-1 ABCA3 as a lipid transropter in pulmonary surfactant biogenesis

◯Nobuya INAGAKI[1,2], Nobuhiro BAN[2,3], Yoshihiro MATSUMURA[2,4]

[1]Kyoto Univ. Grad. Sch. of Med., [2]Akita Univ. Sch. of Med., [3]Chugai Pharmaceutical Co., LTD., [4]Oregon Health & Science Univ.

We showed that ABCA3 protein is expressed predominantly at the limiting membrane of the lamellar bodies in alveolar type II cells. In addition, we showed that expression of ABCA3 in fetal rat lung is dramatically increased just before birth, and that ABCA3 protein expression is induced by glucocorticoids in fetal lung, as is surfactant formation, suggesting involvement of ABCA3 in surfactant formation. Afterward, various mutations in the ABCA3 gene have been reported in newborns with human fatal surfactant deficiency, and we proposed that the ABCA3 gene mutations can be classified into two categories, one involving abnormal intracellular localization (type 1) and the other involving severely impaired activity of ATP-binding and/or hydrolysis of ABCA3 protein (type 2).

To investigate the function and pathophysiological role of ABCA3 protein, we generated *Abca3*-deficient mice by targeting *Abca3*. Full-term *Abca3*$^{-/-}$ newborn pups died within an hour after birth due to acute respiratory failure. Ultrastructural analysis revealed abnormally dense lamellar body-like organelles and no normal lamellar bodies in *Abca3*$^{-/-}$ alveolar type II cells. TLC and ESI/MS analyses of lipids in the pulmonary interstitium showed that phosphatidylcholine and phosphatidylglycerol, which contain palmitic acid and are abundant in normal surfactant lipids, were dramatically decreased in *Abca3*$^{-/-}$ lung. These findings indicate that ABCA3 plays an essential role in pulmonary surfactant lipid metabolism and lamellar body biogenesis, probably by transporting these lipids as substrates.