The role of CFTR in transepithelial liquid transport in pig alveolar epithelia

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In a recent issue of *Am J Physiol Lung Cell Mol Physiol*, Li et al. (22) report that the cystic fibrosis transmembrane conductance regulator (CFTR) is required for cAMP-stimulated liquid absorption in the alveolar epithelia. Using the cystic fibrosis (CF) pig model, they examined the ion and water transport properties of isolated type II alveolar epithelial cells (AEC). Although there have been studies on the role of CFTR in fluid transport in intact rabbit (29), rat (17, 35), mouse lung (9), and cultured human type II AEC (10), Li et al. (22) examined this process in the newly developed pig model for CF, which not only allows for a species comparison but also offers the exciting potential for following ion and fluid transport in an animal model for CF that appears to mimic many of the pathological features of lung disease found in CF patients (1, 27, 28, 30, 36); for an excellent review of the porcine lung as a model for CF see Ref. 32.

Fluid transport and regulation in the lung are critical for a number of reasons including during the transition from fetus to newborn, for lung surface liquid homeostasis, and for recovery from pulmonary edema. Active salt transport typically drives osmotic water transport, and this process promotes fluid clearance from pulmonary edema. Using the cystic fibrosis (CF) pig model, they examined the ion and water transport properties of isolated type II alveolar epithelial cells (AEC). Although there have been studies on the role of CFTR in fluid transport in intact rabbit (29), rat (17, 35), mouse lung (9), and cultured human type II AEC (10), Li et al. (22) examined this process in the newly developed pig model for CF, which not only allows for a species comparison but also offers the exciting potential for following ion and fluid transport in an animal model for CF that appears to mimic many of the pathological features of lung disease found in CF patients (1, 27, 28, 30, 36); for an excellent review of the porcine lung as a model for CF see Ref. 32.

In analyzing liquid transport under open-circuit conditions, Li et al. (22) found that under basal conditions the liquid absorption rate was the same between CFTR+/+ and CFTR−/− type II AEC, indicating that CFTR played no role under basal conditions, and this is consistent with the results of Matthay and colleagues using human type II AEC (10). And as was seen...
with the human type II AEC, CFTR was required for the cAMP-mediated increase in fluid transport (22). The cAMP activation did increase fluid transport in the CFTR+/− type II AEC, but at an approximately four- to fivefold lower level than the CFTR+/+ type II AEC (22). And again, there was no difference in the cAMP-stimulated fluid transport between the CFTR+/+ and CFTR+/− type II AEC. The ex vivo analysis of CFTR+/− newborn pig lungs supported the in vitro findings that CFTR is required for cAMP-stimulated liquid absorption, but not basal fluid transport. To test for the role of CFTR in fluid secretion, Li et al. (22) examined type II AEC grown at an air-fluid interface and found the subphase liquid height was not affected by the presence or absence of CFTR in the type II AEC under basal conditions, whereas cAMP-activation did significantly increase the height in the CFTR+/+ but not the CFTR+/− type II AEC, highlighting that CFTR is a key regulator for both liquid absorption and secretion.

The results are significant because they are consistent with the earlier results of Matthay and colleagues using human type II AEC (10) and illustrate the usefulness of the pig model. Furthermore, this model provides an opportunity to analyze the role CFTR function at later time points during pig development and during the initial stages of CF lung pathology. It is important to remember that the lung pathology in CFTR+/− pigs mimics many of the clinical features of the human disease, including the bacterial infections (32, 36). For the future, closely following how well the model compares to the human disease and understanding how pig and human lungs differ in disease pathology and physiology will be an important consideration for using the pig model for basic ion and liquid transport properties and, perhaps just as importantly, how valid the model is for testing different CF therapeutic interventions.

REFERENCES


