Computational assessment of the structure and function of cystic fibrosis lung disease pathogenesis

By

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Abstract

The pathogenesis of cystic fibrosis (CF) airway disease is not well understood. CF is an autosomal recessive genetic disease. Approximately, 1 in 25 people carry one of over 1,500 disease causing mutations in the gene that encodes the cystic fibrosis transmembrane conductance regulator (Strom et al., 2004) The World Health Organization estimates that 1 in 3,000 European newborns, in Australia 1 in 2,800, and in the United States 1 in 3,500 are born with CF disease (Stoltz et al., 2010). The CF phenotype that causes most of the morbidity and mortality is respiratory disease (Zielenski, 2000).

The aim of this thesis is to investigate CF lung disease pathogenesis from birth to adulthood by analysing the local and global lung structure and function at three time points (birth, 3 weeks of age, and adulthood) in two species (pigs and humans). There is increasing evidence that human CF lung disease, including airflow obstruction, is present earlier than originally thought, even within months after birth (Hoo et al., 2012; Mott et al., 2013; Sly et al., 2009). However, technical and ethical constraints limit our ability to investigate the human lung at even earlier time points.

A porcine CF model was recently generated, in which animals develop lung disease similar to humans with CF. Unexpectedly, before infection and inflammation, newborn CF pigs have airways that are irregularly shaped and have a reduced calibre compared to non-CF pigs. I investigated the effect of the airway abnormalities seen in newborn CF pigs and I examined its effect on the lung function at two time points, birth and three weeks after birth. I used computational fluid dynamics (CFD) and airway geometries obtained by computed x-ray tomography to investigate the effect of early airway structure abnormalities on airflow. I found that newborn CF airways exhibited higher air velocity and resistance compared to non-CF. I also examined particle distribution and deposition. I found that at birth there was

increased particle ventilation fraction to the right lung and higher deposition in the right lower lobe (Awadalla et al., 2014). Three weeks after birth, I found that particle ventilation fraction to the lower lobes decreased while particle ventilation fraction to the right upper lobes increases. This suggests that upper lung lobes disease predominance might be secondary to the effect of congenital airway narrowing in CF. This thesis subsequently investigates progression of CF lung disease pathogenesis in adulthood. I examined the global and local lung structure and function in adult humans with CF. I found that people with CF had lower global pulmonary function compared to healthy subjects. I also found that people with CF had elevated air trapping compared to healthy subjects. I also examined particle distribution and deposition. I found that particle ventilation and deposition to the right upper lobe was also elevated in adults with CF. This was, in part, due to airway structural abnormalities in CF. These findings might have important implications for better understanding the pathogenesis of CF airway disease and the development of inhaled therapeutics in CF.

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