PERSPECTIVES

Regulating the barrier function of airway epithelia. A novel role for CFTR – does it make a difference this time?

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In patients with cystic fibrosis (CF), it is extraordinary that defects in a chloride channel scarcely expressed in airway epithelia, produce severe bronchial infections and eventually respiratory failure. In order to develop effective treatment of CF lung disease, it will be crucial to understand in more detail how the basic molecular defect induces the severe phenotype.

Despite many previous studies assigning multiple roles to the cystic fibrosis transmembrane conductance regulator (CFTR), the precise link between defective transepithelial chloride transport and airway infections remains uncertain, 21 years after the discovery of the CFTR gene (Sheppard & Welsh, 1999).

In contrast to earlier studies, LeSimple *et al.* (2010), in a recent issue of *The Journal of Physiology*, approached the problem by the paracellular pathway, a road less travelled by CF researchers. Their results suggest a novel role for CFTR in modulating paracellular transport and airway epithelial barrier function.

Airway epithelial integrity and normal barrier function depend on tight junctions (TJs) located apically in the paracellular space. These junctions contain transmembrane proteins such as claudins, occludins, JAM and E-Cadherin that extend into the intercellular space and regulate the flux of ions and solutes travelling the paracellular pathway (Anderson & Van Itallie, 2009; Furuse, 2010). TJ proteins also regulate the polarity and differentiation of airway epithelia, both of which are required for efficient clearance of particles and lung defence (Bals & Hiemstra, 2004).

In their excellent paper, LeSimple *et al.* found that the expression of CFTR, but not the commonest cystic fibrosis mutation ΔF508, was associated with increased transepithelial resistance (TER) in CF airway epithelia and that this effect was independent of channel function. They concluded that CFTR trafficking was required for the normal organization and function of tight junctions and that the loss of CFTR leads to abnormally low TER and loss of epithelial integrity. If this were true in the sodium hyperabsorbing CF airway *in vivo*, the paracellular pathway would allow increased flux of chloride and water, leading to airway surface liquid dehydration and thick mucus accumulation. Increased paracellular permeability could also allow bacteria or their toxins to access critical receptors at the basolateral membrane thereby inducing epithelial injury and inflammation. Based on this hypothesis, it is possible that CFTR is crucial for normal lung defence, regulating normal TJ assembly, and early epithelial development and differentiation. Therefore, lack of CFTR could lead to severe airway epithelial dysfunction, as observed in the CF lung.

This notion might indeed be supported by studies showing that the function of TJ proteins is important to defend airway epithelia against pathogens. Zulianello *et al.* (2006) used electron microscopy to show that *Pseudomonas aeruginosa* were present in the intercellular space. They also found that TER decreased during infection. The data indicated that *Pseudomonas aeruginosa* invaded the epithelia by penetrating the paracellular space, not by endocytosis, suggesting that disruption of TJs occurred during bacterial invasion. Subsequent access to critical basolateral receptors could enable the bacteria to induce epithelial injury and inflammation. Assuming that CFTR regulates TJ function and maintains TER as indicated by LeSimple *et al.* (2010), loss of CFTR could predispose the epithelium to paracellular invasion by pathogenic bacteria, resulting in chronic epithelial injury and inflammation.

Interestingly, earlier studies indicate that regulation of TJs by CFTR might be clinically relevant. Several clinical trials show that the antibiotic azithromycin is beneficial in CF patients independent of its antimicrobial activity (e.g. Saiman *et al.* 2003). Possible mechanisms explaining this effect include anti-inflammatory effects, effects on sputum rheology, biofilm production and TJ expression. Recently, azithromycin was shown to increase TER in airway epithelia, and to maintain TER during *Pseudomonas aeruginosa* infection *in vitro* by affecting TJ protein expression (Halldorsson *et al.* 2010). If TER is indeed low in CF airway epithelia *in vivo*, as suggested by LeSimple *et al.* (2010) it is possible that azithromycin compensates for the loss of CFTR in CF patients by increasing TER and improving epithelial integrity and barrier function.

The novel results presented by LeSimple *et al.* (2010) suggest that CFTR is required for airway epithelial integrity. This might be part of the missing link between defective CFTR and bronchial infections that characterize CF lung disease. The data are also a reminder that the function of CFTR in normal airway epithelia should be further explored, focusing on the interaction of CFTR with TJ proteins and the paracellular pathway. Perhaps our thoughts should take that road more often, hoping to make all the difference.

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