JOURNAL CLUB

SPLUNC1: link between acidity and dehydration of the airway surface liquid in CF

Short palate lung and nasal epithelial clone 1 (SPLUNC1) is the most abundant secreted protein in the airways and helps maintain a normal airway surface liquid (ASL) volume through its regulation of the epithelial Na^+ channel (ENaC). In cystic fibrosis (CF), it has been proposed that increased Na^+ absorption by ENaC contributes to ASL depletion, despite the presence of SPLUNC1.

The study by Garland *et al* showed the pH of nasal secretions from CF subjects (pH~6.5) was more acidic than non-CF subjects (pH~7.2), consistent with previous studies of CF ASL. Re-creating such conditions *in vitro*, the investigators found that alkalinising the ASL across CF airway epithelial cultures prevented fluid hyperabsorption, an effect absent in SPLUNC1-depleted cultures. SPLUNC1 binding to the cell surface, which was dependent on ENaC expression, was reduced under acidic conditions. The authors reasoned the acidity of the CF airways may alter the ability of SPLUNC1 to bind to ENaC, explaining why it is unable to limit ENaC activity in CF. This hypothesis was supported by demonstrating that deletion of two pH-sensitive salt bridges in the SPLUNC1 protein rendered SPLUNC1 binding at the cell surface pH-insensitive, restoring normal ENaC regulation and ASL volume under acidic conditions.

In addition to identifying the pH-dependent activity of SPLUNC1 as an important link between the acidity of the CF airways and the dysregulation of ENaC, the study may also provide evidence of how the cystic fibrosis transmembrane conductance regulator (CFTR) indirectly regulates ENaC activity, since aberrant CFTR-dependent HCO_3^- secretion is proposed to contribute to the acidity of the CF ASL. Raising CF ASL pH could restore normal mucosal hydration, as well as other vital pH-dependent processes such as bacterial killing by antimicrobials, and thus warrants further investigation as a potential avenue for CF therapy.

▶ Garland AL, Walton WG, Coakley RD, *et al*. Molecular basis for pH-dependent mucosal dehydration in cystic fibrosis airways. *Proc Natl Acad Sci USA* 2013;110:15973–8.

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