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Original Article

Ion channels as targets to treat cystic fibrosis lung disease

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Abstract

Lung health relies on effective mucociliary clearance and innate immune defence mechanisms. In cystic fibrosis (CF), an imbalance in ion transport due to an absence of chloride ion secretion, caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) and a concomitant sodium hyperabsorption, caused by dyregulation of the epithelial sodium channel (ENaC), results in mucus stasis which predisposes the lungs to cycles of chronic infection and inflammation leading to lung function decline.

An increased understanding of CFTR structure and function has provided opportunity for the development of a number of novel modulators targeting mutant CFTR however, it is important to also consider other ion channels and transporters present in the airways as putative targets for drug development. In this review, we discuss recent advances in CFTR biology which will contribute to further drug discovery in the field. We also examine developments to inhibit the epithelial sodium channel (ENaC) and potentially activate alternative chloride channels and transporters as a multi-tracked strategy to hydrate CF airways and restore normal mucociliary clearance mechanisms in a manner independent of CFTR mutation.

Keywords: Cystic fibrosis; CFTR; ENaC; Ion channel; Proteases; Airways hydration; Ion transporter; Anion exchanger

1. Introduction

Cystic fibrosis (CF) is the most common life-limiting, hereditary condition which affects Caucasian populations with morbidity and premature mortality associated predominantly with chronic lung disease [1]. It is caused by mutations in the CFTR (cystic fibrosis transmembrane conductance regulator) gene which encodes an ATP-dependent, apical membrane-associated chloride ion channel which plays a pivotal role in the regulation of ion secretion and absorption across epithelial cells. There are currently over 2000 known CFTR mutations, although fewer than 20 mutations occur at a frequency of >0.1% and only 5 at a frequency >1% [2]. These mutations are grouped into 6 classes depending on the degree to which the *CFTR* mutation affects CFTR quantity, transport to or function at the cell surface, however as our understanding of CFTR structure and function increases, further sub- or re-classification may assist current aspirations for a fully personalized medicines approach to this disease [2].

The CF phenotype, which in addition to the lungs, affects the pancreas, liver, kidneys and intestines is however not just the result of abnormal CFTR-mediated Cl^- secretion. Indeed, a loss of CFTR function, can also affect a number of other key

Abbreviations: ABC, ATP Binding Cassette; AE, anion exchanger; ASL, airways surface liquid; ATP, adenosine triphosphate; CAP, channel activating protease; CaCC, calcium activated chloride channel; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; ΔF508, CFTR mutation encoding a deletion of phenylalanine at position 508; ENaC, epithelial sodium channel; HAT, human airways trypsin-like protease; NBD, nucleotide binding domain; NHE, Na^+/H^+ exchanger; NKCC1, Na-K-Cl cotransporter; PKA, protein kinase A; siRNA, small-interfering RNA; UTP, uridine triphosphate

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ion channels, transporters and pumps which contribute to lung health by working together to ensure effective mucociliary clearance and innate immune defence mechanisms through the optimization of cell surface hydration, charge and pH [3]. In particular, the build-up of, and inability to clear, mucus in CF airways is due to an observed reduction in airway surface liquid (ASL) volume which is fundamentally a result of sodium hyperabsorption caused by dysregulation of the epithelial sodium channel (ENaC) in the cells lining the airways [4].

In this Review, we summarise the key areas covered in Symposium 6: *Cell Physiology and Ion Transport*, and highlight in particular recent developments in our understanding of CFTR structure and function as well as novel strategies to target ENaC. Other ion channels, such as the TMEM16A chloride channel and the calcium-activated potassium channel KCa3.1, and ion transporters are also presented as alternative pathways to restore surface hydration and pH in CF airways by increasing chloride and/or bicarbonate secretion. These approaches, summarized in Fig. 1, offer very attractive targets for pharmacological intervention, and importantly could complement current drug therapies focused on the correction of CFTR mutations which together could result in the development of a broader arsenal of disease-modifying treatments for CF.

2. Recent developments in our understanding of CFTR structure and function

The CFTR chloride channel is a member of the family of ATP Binding Cassette (ABC) proteins, and is built from two homologous halves each containing a transmembrane domain (TMD) followed by a cytosolic nucleotide binding domain (NBD). In CFTR these two halves are linked by the unique cytosolic regulatory (R) domain [5] which inhibits channel activity unless phosphorylated by cyclic AMP-dependent protein kinase (PKA) [6,7]. Unlike in other ABC proteins which are mostly active transporters, in CFTR the TMDs form a transmembrane anion-selective pore. Nevertheless, the molecular motions that drive uphill substrate translocation in ABC proteins

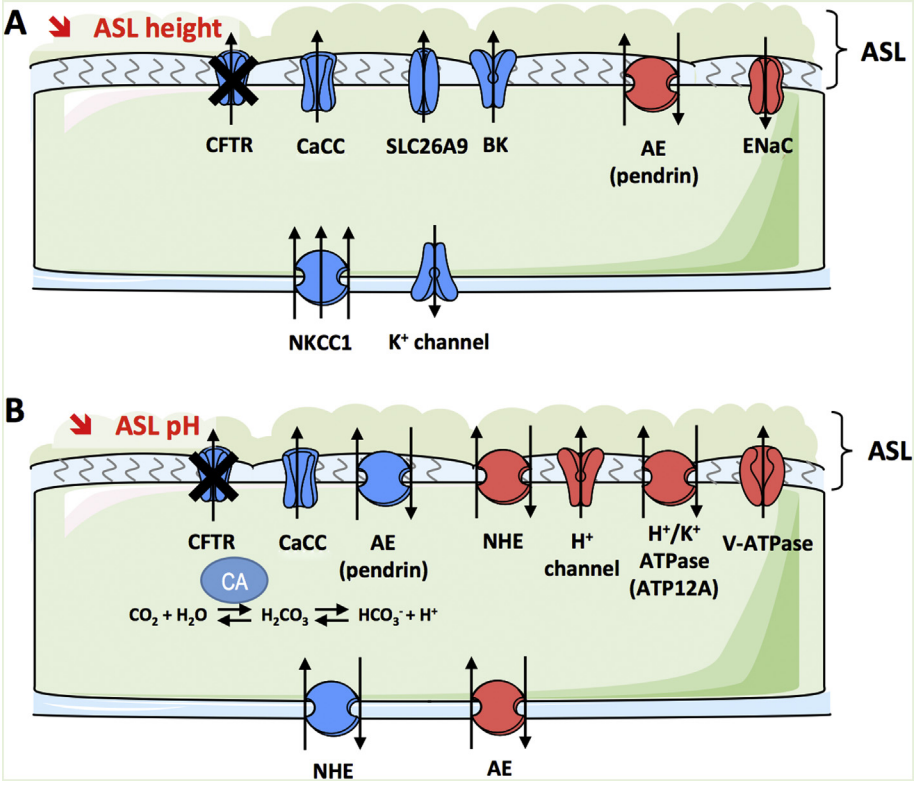

Fig. 1. Alternative channels and transporters for the regulation of ASL height (A) and ASL pH (B), in CF. A. Modulation of Cl^- and Na^+ transport involves increasing anion and fluid secretion (by activating the blue channels and transporters) and/or decreasing Na^+ and fluid absorption (by inhibiting the red channels and transporters). Anion secretion can be increased by activating Ca^{2+}-activated Cl^- channels (CaCC), such as TMEM16A, or Cl^- channels, such as SLC26A9 on the apical membrane. K^+ secretion on the apical surface can also regulate ASL volume. On the basolateral membrane, a Na-K-Cl cotransporter (NKCC1) is the limiting factor for Cl^- entry into the cells and K^+ recycling through basolateral K^+ channels, such as KCNQ1, provides the driving force for transcellular Cl^- secretion. Inhibition of ENaC reduces Na^+ hyperabsorption and fluid absorption which increases ASL volume. Inhibition of pendrin, an anion exchanger (AE) has also been shown to increase airways hydration. B. Modulation of HCO_3^- and H^+ transport involves increasing apical HCO_3^- secretion or basolateral H^+ secretion (through blue channels and transporters) and/or decreasing apical H^+ secretion and basolateral bicarbonate (HCO_3^-) secretion (through red channels and transporters). Theoretically, activation of any apical HCO_3^- transporter could increase ASL pH, such as CaCC or pendrin. Inhibiting apical Na^+/H^+ exchangers (NHE; such as NHE3/SLC9A3, a modifier gene associated with severity of CF lung disease), H^+ channels, H^+/K^+-ATPase or V-ATPase could also increase ASL pH. In the cytoplasm, the carbonic anhydrase (CA) is involved in the CO_2/HCO_3^- buffering system and could contribute to the regulation of ASL pH by increasing intracellular HCO_3^- concentration. In the basolateral membrane, activating NHE could prevent apical H^+ secretion and inhibiting anion exchange could sustain intracellular HCO_3^- concentration required for its apical secretion. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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