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Review Article

Cystic fibrosis — What are the prospects for a cure?

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ABSTRACT

Significant improvements in the treatment of cystic fibrosis over the last few decades have altered this lethal disease in children to a multisystem disorder with survival into adult life now common. In most developed countries the numbers of adult cystic fibrosis patients outnumber children. This is mainly due to improvements in care during early life. The principal cause of morbidity and mortality is pulmonary disease, and so the focus of new treatments has targeted the lungs. Identification of the underlying gene defect in the cystic fibrosis transmembrane conductance regulator has ushered in a new era in cystic fibrosis research, with prospects of a cure. In this article, we review the most exciting recent advances that correct defects in cellular processing, chloride channel function and gene therapy.

1. Background

Cystic fibrosis (CF) is the commonest life-limiting autosomal recessive condition in Europe affecting 1 in 2000 to 3000 newborns, with a carrier rate of 4% in the United Kingdom, rising to as much as 70% in northern, western, and north-eastern Europe [1–3]. It is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, found on the surface of cells in a variety of tissues including the lungs, gut and pancreas, where it functions as a regulated chloride ion channel. Loss or defective function of the gene product gives rise to disease. Viscous secretions predispose to pulmonary and pancreatic disorders [4]. In the lungs, tenacious secretions predispose to repeated infections, leading to bronchiectasis, respiratory failure and cor pulmonale. Exocrine pancreatic insufficiency develops with occlusion of the pancreatic duct by viscous secretions, and manifest clinically as steatorrhoea. In the latter stages of disease, pancreatic endocrine dysfunction gives rise to diabetes mellitus. Median predicted survival is now over 40 years and in the United Kingdom, 57.6% of CF patients are classified as adults with 9.1% aged living beyond 40 years [5].

2. Molecular basis of cystic fibrosis

In health, respiratory epithelium is lined by a thin layer of fluid referred to as the airway surface liquid (ASL) (Fig. 1). It comprises periciliary liquid over which lies the mucus layer, secreted by goblet and Clara cells. Mucus traps microorganisms before being cleared by the muco-ciliary escalator. Periciliary fluid secretion is tightly regulated by absorption of sodium by the apical membrane epithelial sodium channel (ENaC), together with active chloride secretion by the CFTR to maintain the ASL in which the cilia bathe [6].

In CF, the gene mutation resides on chromosome 7 in the region of 7q31.2 which codes for the CFTR protein. Almost 2000 mutations have been identified, divided into 5 classes (Fig. 2) [7]. The most prevalent abnormality is a deletion in delta F508 (dF508). The mutation alters the secondary and tertiary structure of the protein, so that chloride channels fail to open in response to elevated cAMP in epithelial cells. Defective expression, trafficking or function of CFTR leads to impaired secretion of chloride and an increase in sodium absorption. This causes depletion of the airway surface liquid and, in turn, to defective mucociliary action and reduced mucus clearance. This encourages bacterial colonisation, recurrent infections, chronic inflammation and irreversible damage to the airway epithelium.

In the 1980s, children with CF rarely lived beyond adolescence. Innovative management strategies based on daily chest physiotherapy to facilitate mucus clearance, correct nutrition, and early intervention with antimicrobials to stem infection promptly have improved life expectancy to the 4th decade [8]. Breakthroughs in antibiotics, anti-inflammatories, mucolytics and pancreatic replacement only treat the manifestations of the disease so the ion channel defect remains. In recent years, fundamental knowledge of molecular and cell biology has helped to define the underlying ion channel defect, and increased the prospects of targeted therapy. This article reviews the most promising therapeutic avenues, which include correcting defects in cellular processing, chloride channel function and replacing the defective gene.

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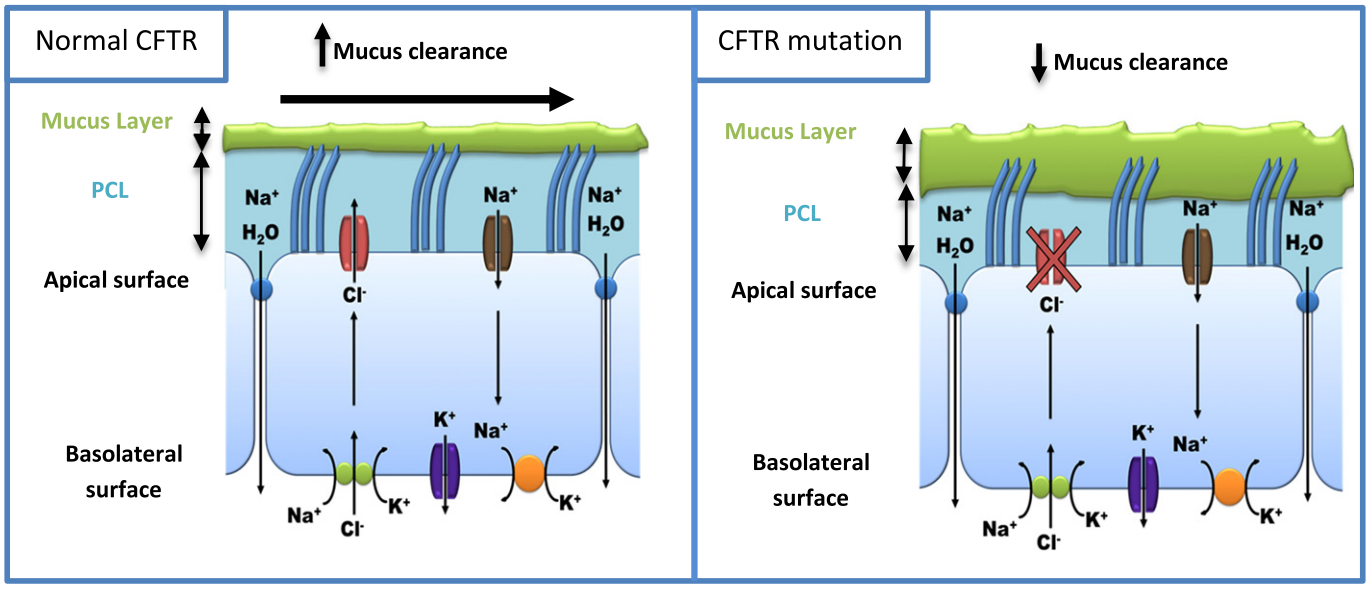

Fig. 1. The defect in cystic fibrosis. A mutation in the CFTR gene prevents Cl^- being secreted and there is unrestrained Na^+ absorption causing the ASL to become dehydrated, leading to defective mucous clearance.

2.1. Ion channel modulators

These drugs aim to correct the underlying defect in cellular production and/or potentiate chloride movement across the ion channel. Given the heterogeneity of effects on the CFTR by different mutations, ion channel modulators can only be targeted against specific mutations. The most common CFTR malfunctions can be targeted using this strategy which has led to the development of several drugs. One of these has been approved by the FDA and two drugs are the focus of major clinical trials. Drug categories include potentiators which target defective regulation and impaired conductance, correctors that address impaired processing and read-through therapy which overcomes defective production of the CFTR.

3. Potentiators

Ivacaftor (Kalydeco), an oral potentiator produced by Vertex pharmaceuticals, is the only drug in its class currently licensed for use in clinical practice. Known investigationally as VX770, it directly affects CFTR mutation G551D by enhancing gating at the cell surface. This increases the time that activated CFTR channels remain open at the cell surface. In vitro studies identified that Ivacaftor increases CFTR channel opening and promotes apical surface fluid and cilia beating [9]. A randomised, double-blind, placebo-controlled trial validated the safety and adverse event profile of Ivacaftor in 39 patients aged 18 years and over who possessed the G551D mutation [10]. Minor side effects such as fever, cough, nausea and rhinorrhoea resolved spontaneously without drug cessation. There was a marked reduction in sweat chloride concentration, with some subjects outside the diagnostic range for CF. Nasal potential difference (significantly more negative in CF due to increased luminal sodium absorption) and lung function improved.

Two major long-term randomised placebo-controlled phase 3 trials have been conducted in G551D CF patients. They assessed the efficacy of Ivacaftor in 161 children aged 12 years and over [11]. Mean forced expiratory volume in the first second (FEV_1) increased by 10.5% at 24 weeks, with improvement sustained at 48 weeks. Significant improvements in the secondary clinical end points were a 55% reduction in the risk of developing an infective pulmonary exacerbation, improvement in respiratory symptoms assessed by the Cystic Fibrosis Questionnaire revised (CFQ-R) score and weight gain. The mechanism for weight gain is unclear but may be due to improved CFTR function in the gut [11]. Ivacaftor was discontinued in 13% compared to 6% in the placebo group, due to adverse effects including liver dysfunction, atrioventricular heart block, haemoptysis, pulmonary exacerbation and panic attacks.

Next, an open-labelled trial showed that the effects on the FEV_1 were maintained at 60 weeks, with 43.5% of patients receiving Ivacaftor, free of pulmonary infection [12]. The randomised, double-blind, placebo-controlled phase 3 ENVISION trial evaluated the safety and efficacy of Ivacaftor in younger children (age 6–11 years) with at least one G551D mutation [13]. The study confirmed that efficacy of Ivacaftor extended to this younger cohort, with a statistically significant increase in FEV_1, a decrease in sweat chloride, and weight gain.

Beneficial effects of Ivacaftor have been limited to individuals with the G551D class 3 mutation, which represents only 3% of the burden of CF. Although in vitro studies demonstrate that it increases chloride secretion approximately 10-fold in cultured human CF bronchial epithelial cells (HBECs) carrying the dF508 processing mutation, this has not been replicated in vivo [14]. No significant change in FEV_1 or sweat chloride concentration has been demonstrated. Failure of Ivacaftor to modify CFTR function may be explained by misfolding of the protein associated with this mutation preventing translocation of CFTR at the cell surface.

4. Correctors

Lumacaftor, known investigationally as VX-809, is a channel corrector that allows the dF508 CFTR to bypass proteomic degradation and increases trafficking of the protein to the epithelial cell surface [15]. Its efficacy was validated in cultured human CF bronchial epithelial cells isolated from patients with CF homozygous for dF508 [16]. Lumacaftor improved dF508-CFTR processing in the endoplasmic reticulum and raised chloride secretion to approximately 14% of non-CF human bronchial epithelial cells, a level that corresponds with milder forms of the disease. These encouraging results prompted a 28-day phase 2 trial in adult CF patients with this gene mutation [17]. The drug produced a dose-dependent reduction in sweat chloride levels compared to placebo, but there was no significant improvement in CFTR function in the nasal epithelium by measuring nasal potential difference, nor were there statistically significant changes in lung function or patient-reported outcomes.