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New treatments targeting the basic defects in cystic fibrosis

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Summary

Cystic fibrosis (CF) is a monogenic autosomal recessive disorder affecting around 75,000 individuals worldwide. It is a multi-system disease but the main morbidity and mortality is caused by chronic lung disease. Due to newborn screening, a multidisciplinary approach to care and intensive symptomatic treatment, the prognosis has dramatically improved over the last decades and there are currently more adults than children in many countries. However, CF is still a very severe disease with a current median age of life expectancy in the fourth decade of life. The disease is caused by mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR)* gene which encodes the CFTR protein, a protein kinase A-activated ATP-gated anion channel that regulates the transport of electrolytes such as chloride and bicarbonate. More than 2000 mutations have been reported, although not all of these have functional consequences. An enormous research effort and progress has been made in understanding the consequences of these mutations on the CFTR protein structure and function, and this has led to the approval of two new drug therapies that are able to bind to defective CFTR proteins and partially restore their function. They are mutation-specific therapies and available at present for specific mutations only. They are the first personalized medicine for CF with a possible disease-modifying effect. A pipeline of other compounds is under development with different mechanisms of action. It is foreseeable that new combinations of compounds will further improve the correction of CFTR function. Other strategies including premature stop codon read-through drugs, antisense oligonucleotides that correct the basic defect at the mRNA level or gene editing to restore the defective gene as well as gene therapy approaches are all in the pipeline. All these strategies are needed to develop disease-modifying therapies for all patients with CF.

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Introduction

Cystic fibrosis (CF) is an autosomal recessive multi-organ disease affecting approximately 75,000 individuals worldwide [1]. The main clinical features are exocrine pancreatic insufficiency and bronchiectasis with chronic airway infection leading to respiratory failure and premature death. The disease was described in 1938 [2] and although the biochemical basis of CF was not identified for 50 years, the disease was known to be associated with abnormalities of chloride and sodium transport in several epithelia [3,4]. In 1989, the *cystic fibrosis transmembrane conductance regulator* (*CFTR*) gene was cloned [5] and the CFTR protein identified as a chloride channel [6]. This led to a growing research output on the basic defects in CF: the *CFTR* gene and mutations, and the CFTR protein's maturation, structure, function and interactions with other ion channels. The mainstay of treatment in CF is symptomatic and focuses on compensating for exocrine pancreatic insufficiency with pancreatic enzymes, fat-soluble vitamins and high caloric intake; and slowing lung disease progression with inhaled and physical therapies that improve airway clearance, and antibiotic therapy [7]. The goals of new approaches to therapy include the development of drugs that correct the basic defect in CF that might delay the progression or prevent respiratory disease if given early enough in life. Since 2012, and twenty-three years after the cloning of the *CFTR* gene, two new drugs aimed at correcting defective CFTR protein have been made available to patients bearing specific *CFTR* mutations and they are the first personalized medicine in CF. Improvements on these approaches as well as many other corrective strategies are currently under clinical investigation.

In this review, we will discuss the basic defects in CF that might be targeted to develop disease-modifying treatments, and provide an overview of the two currently available CFTR modulator therapies. Lastly, we will review other strategies currently in development to restore robust CFTR function along with some discussion around the remaining challenges that need to be overcome before such disease-modifying drugs are made available to all patients with CF.

Cystic fibrosis basic defects that are possible therapeutic targets

CFTR gene and mRNA

The *CFTR* gene was cloned in 1989 by using chromosome walking and jumping, and linkage disequilibrium analysis [5]. The gene comprises 27 coding exons, spanning over 250 kb on the long arm of chromosome 7, and the transcript is 6.5 kb. To date, around 2000 *CFTR* mutations have been described. However, a molecular alteration in the DNA sequence does not necessarily lead to a defective CFTR protein and clinical disease. Around 250 variants have evidence supporting a disease-causing effect [8,9]. Only ~20 mutations occur at a worldwide frequency above 0.1% in CF patients, and determining the disease liability of very rare mutations is often difficult [10]. As CF is a genetic disease due to mutations in a single gene, one approach to treat the basic defect would be to develop oligonucleotide-based drugs to bypass or correct the DNA or mRNA defects in order to produce a normal CFTR protein (*figure 1*). These strategies known as gene therapy, gene editing or RNA repair have been the subject of extensive research since the cloning of the *CFTR* gene. As oligonucleotides are poorly suited for oral or systemic delivery, these approaches are likely to remain restricted to local respiratory treatment via aerosol. The great advantage of the gene therapy approach is that it is not restricted to specific mutations and airway administration of normal cDNA could theoretically treat airway disease of all patients. Successes and pitfalls of targeting DNA or mRNA defects to treat CF are described later in this review.

CFTR protein

The CFTR protein is an anion channel expressed at the apical membrane of many epithelial cells. It allows chloride and bicarbonate transport thereby creating an osmotic gradient for fluid secretion. The CFTR protein is a member of the ATP-binding cassette (ABC) family of transporter proteins. They are characterized by two membrane-spanning domains (MSD1 and MSD2) which form the channel pore, and two nucleotide-binding domains (NBD1 and NBD2) which bind and hydrolyse ATP. CFTR has an additional regulatory domain which regulates channel opening and closing (for review: [11]) (*figure 2*). When open or activated, the CFTR protein allows passive diffusion of chloride or bicarbonate ions down their electrochemical gradient. The CFTR protein also has many other roles such as inhibition of sodium transport through the epithelial sodium channel (ENaC) and regulation of other chloride channels. It is also thought to interact with cellular pathways related to inflammation [12].

Mucociliary clearance is a primary innate defense mechanism that helps to protect healthy airways from accumulation of inhaled particles including bacteria [13]. The airway epithelium is mainly composed of ciliated cells on which lies an airway surface liquid consisting of an overlying mucus layer and a periciliary liquid layer. The mucus layer is produced by submucosal glands and goblet cells and contains endogenous antimicrobial agents that kill bacteria. The periciliary liquid layer produced by the airway epithelium is crucial because it provides a low-viscosity solution in which cilia can beat rapidly [12,14]. Thus, in the healthy situation, the cilia beat within the periciliary liquid and sweep bacteria trapped in mucus out of the lung.

Glossary

CF	**Cystic fibrosis**
CFTR	**Cystic Fibrosis transmembrane Conductance Regulator**
ENaC	**Epithelial sodium channel**
ppFEV$_1$	**percent predicted forced expiratory volume in one second**