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New horizons for cystic fibrosis treatment

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ABSTRACT

Cystic fibrosis is an inherited multi-system disease associated with chronic lung infection, malabsorption, salt loss syndromes, male infertility and leading to numerous comorbidities. The landscape in cystic fibrosis care has changed markedly with currently more adult patients than children in many countries. Over 2000 different mutations in the *CFTR* gene have been reported and the majority are extremely rare. Understanding how *CFTR* mutations translate to disturbed synthesis or function of the CFTR protein has opened the way to 'personalized' treatments to correct the basic defect. The first 2 drugs have reached the clinic: a CFTR potentiator to augment CFTR channel function, and the combination of this potentiator with a corrector to increase CFTR expression at the cell membrane. To obtain robust correction of CFTR expression at the cell membrane, combinations of correctors with additive efficacy are under investigation. Other mutation type-specific treatments under clinical investigation are premature stop codon-read through drugs and antisense oligonucleotides that correct the basic defect at the mRNA level. Restoring the defective gene by gene editing can already be achieved ex vivo. Mutation agnostic treatments are explored as well: stabilizing CFTR expression at the cell membrane, circumventing the CFTR channel by blocking or activating other ion channels, and gene therapy. Combinations of these therapies can be anticipated. The pipeline of corrective strategies under clinical investigation is increasing continuously and a rising number of pharmaceutical companies are entering the field.

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1. Introduction

Cystic fibrosis (CF) is the most common life-shortening genetic disease in the caucasian population, affecting approximately 75,000 individuals worldwide (Farrell, 2008). It is an autosomal recessive disorder caused by mutations in the cystic fibrosis transmembrane conductance regulator gene (*CFTR*) (Riordan et al., 1989). The *CFTR* gene encodes the CFTR protein which is a chloride channel expressed in

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Abbreviations: CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; MSD, membrane-spanning domain; NBD, nucleotide-binding domain; FEV1, forced expiratory volume in 1 s.

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many epithelial cells. CF is a multi-system disease affecting organs and tissues where CFTR is expressed. The most common clinical features are exocrine pancreatic insufficiency and bronchiectasis with chronic airway infection leading to respiratory failure and premature death. Current treatments are mainly symptomatic focusing on compensating for exocrine pancreatic insufficiency with pancreatic enzymes, and slowing lung disease progression with airway clearance techniques and antibiotic therapy (Cohen-Cymberknoh, Shoseyov, & Kerem, 2011). New therapies aiming at treating the downstream complications of CFTR dysfunction are in development including novel inhaled antibiotics, anti-inflammatory drugs, agents to enhance mucociliary clearance and nutritional/pancreatic replacement therapies. But since 2012, two new drugs called CFTR modulators with the aim of restoring CFTR protein function have become available, and several other CFTR modulators are in development. In this review, we will focus on these CFTR modulators that are likely to dramatically change CF care and prognosis over the coming decades. However, drugs allowing better restoration of CFTR function are still needed and development of these disease-modifying drugs for all patients with CF especially those with rare mutations is challenging.

2. Clinical manifestations and current symptomatic treatments

CF-related symptoms appear throughout life, with great overlap and variability of symptoms and timing from patient to patient. The main clinical features of CF reflect gastrointestinal and respiratory symptoms. Gastrointestinal symptoms are mainly due to pancratic insufficiency. Typical signs are greasy stools and poor weight gain. Pancratic insufficiency leads to steatorrhea, fat-soluble-vitamin deficiency and malnutrition (Gelfond & Borowitz, 2013). Seventy years ago, when CF was described, children died of malnutrition. When pancreatic replacement enzyme therapy became available in the 1950s, CF prognosis began to change. CF lung disease is now the major cause of morbidity and mortality. It is characterised by chronic airway infection and inflammation leading to bronchiectasis. Daily symptoms as disease progresses are cough and sputum production. Patients with CF develop bacterial infections which can be cleared initially with antibiotic therapy. Later, persistent bacterial infection of the airways occurs. One of the most frequent pathogens isolated in the CF airways is *Pseudomonas aeruginosa* and infection with *P. aeruginosa* is associated with a worse prognosis (Lund-Palau et al., 2016). Intermittent episodes of acute worsening of respiratory symptoms called pulmonary exacerbations are treated by intensification of daily therapies and antibiotics in order to restore the lung function commonly lost during an exacerbation. Other pathogens such as *Staphylococcus aureus* including Methicillin-Resistant *S. aureus*, Gram-negative bacterial species, non-tuberculous mycobacteria or *Aspergillus* species may also be isolated from the airways. Acute respiratory complications such as pneumothorax or hemoptysis may occur. Chronic lung infection and airway obstruction lead to a progressive decline in airway function and respiratory failure which is the main cause of death. CF is a multiorgan disease and many comorbities may occur such as salt loss syndromes, diabetes, gall stones, cholangiectasis, cirrhosis, chronic sinusitis and nasal polyps, bone disease or infertility.

The main principles of CF treatment were established as early as the 1960s, and steadily evolved with the better understanding of the disease and the availability of new drugs. They are based on a holistic approach to care and intensive symptomatic treatment (Cohen-Cymberknoh et al., 2011). Specialised CF centers formed by a multidisciplinary team experienced in CF have become the model of care for patients with CF (Conway et al., 2014). The principles of symptomatic treatment are maintenance of good nutrition, enhancement of mucociliary clearance, prevention and aggressive treatment of pulmonary infection, treatment of airway inflammation, and early identification and treatment of complications. CF has benefited from the development of new and effective treatments such as antibiotics against *P. aeruginosa*, including inhaled antibiotics. As a result of this structured follow-up in dedicated centers and implementation of aggressive and complex treatments, projected life expectancy for patients with CF has increased from a matter of months to nearly 50 years (MacKenzie et al., 2014). Similarly, in several countries the number of adults with CF is currently larger than the number of children with CF (Burgel et al., 2015). However, the expected survival of a child born today with CF is still only 50 years and the current median age of death is around 30 years with respiratory failure being the common cause of death (ECFS Patient Registry Report 2013, available: https://www.ecfs.eu/projects/ecfs-patient-registry/annual-reports).

3. Basic defects in CF and theoretical approach to correct them

Cystic fibrosis is caused by mutations in the *CFTR* gene which was identified in 1989. It comprises 27 coding exons, spanning over 250 kb on chromosome 7 (Riordan et al., 1989). It encodes the CFTR protein which is an anion channel of primary importance for chloride and bicarbonate transport. The CFTR protein is expressed at the apical membrane of many epithelial cells with direct relationships between abnormal expression and CF pathology. When open or activated, it allows passive diffusion of chloride ions down their electrochemical gradient. It has also many other roles such as inhibition of sodium transport through the epithelial sodium channel and regulation of other chloride channels. It is also thought to interact with cellular pathways related to inflammation (Cohen & Prince, 2012; Stoltz, Meyerholz, & Welsh, 2015). The CFTR protein is a member of the ATP-binding cassette (ABC) protein superfamily. It is characterised by 2 membrane-spanning domains (MSD1 and MSD2) which anchor the protein in the plasma membrane. Each is conjoined to a nucleotide binding domain (NBD1 and NBD2) which binds and hydrolyses ATP. Unique to CFTR is a regulatory domain which has to be phosphorylated by the cAMP-dependent protein kinase for channel gating by ATP (Fig. 1) (for review: (Hwang & Kirk, 2013).

To date, around 2000 *CFTR* mutations have been described. However, a molecular alteration in the DNA sequence does not equal a potential defect in expression or function of the protein product. Around 250 variants have evidence supporting a disease-causing effect (Castellani et al., 2008; Sosnay et al., 2013). Mutations in the *CFTR* gene have been grouped into six classes according to their effects on the maturation and function of the CFTR protein (Welsh & Smith, 1993; Zielenski & Tsui, 1995) (Fig. 2):

I. Class I mutations group mutations that result in no protein production. They comprise premature stop codon mutations (e.g. G542X), frameshift mutations or large deletions. These mutations are present in around 10% of patients worldwide.
II. Class II mutations cause protein trafficking defects which may result in premature degradation of CFTR. The most common mutation, F508del, belongs to this class. It is present on at least one allele in 70% of patients with CF.

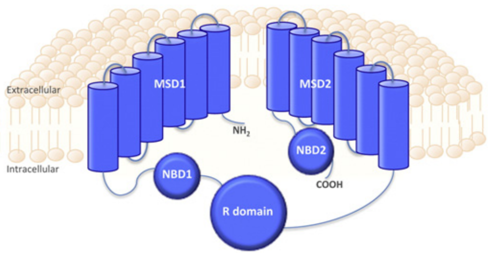

Fig. 1. Diagram of the CFTR protein structure. The two transmembrane spanning domains (MSD1 and MSD2) form the channel pore. Opening of the pore and anion flow through it is powered by cycles of ATP binding and hydrolysis at the two ATP-binding sites located on the intracytoplasmic nucleotide-binding domains (NBD1 and NBD2). Phosphorylation of the intracellular regulatory domain (R domain) stimulates CFTR function by enhancing ATP-dependent channel gating at the NBDs.

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