The International Journal of Biochemistry & Cell Biology xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

The International Journal of Biochemistry & Cell Biology

journal homepage: www.elsevier.com/locate/biocel

Review

Cystic fibrosis: Toward personalized therapies☆

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ARTICLE INFO

Article history:
Received 27 December 2013
Received in revised form 10 February 2014
Accepted 12 February 2014
Available online xxx

Keywords:
Cystic fibrosis
Personalized medicine
Organoids
CFTR correctors
CFTR potentiators

ABSTRACT

Cystic fibrosis (CF), the most common, life-threatening monogenetic disease in Caucasians, is caused by mutations in the CFTR gene, encoding a cAMP- and cGMP-regulated epithelial chloride channel. Symptomatic therapies treating end-organ manifestations have increased the life expectancy of CF patients toward a mean of 40 years. The recent development of CFTR-targeted drugs that emerged from high-throughput screening and are capable of correcting the basic defect promises to transform the therapeutic landscape from a trial-and-error prescription to personalized medicine. This stratified approach is tailored to a specific functional class of mutations in CFTR, but can be refined further to an individual level by exploiting recent advances in *ex vivo* drug testing methods. These tests range from CFTR functional measurements in rectal biopsies donated by a CF patient to the use of patient-derived intestinal or pulmonary organoids. Such organoids may serve as an inexhaustible source of epithelial cells that can be stored in biobanks and allow medium- to high-throughput screening of CFTR activators, correctors and potentiators on the basis of a simple microscopic assay monitoring organoid swelling. Thus the recent breakthrough in stem cell biology allowing the culturing of mini-organs from individual patients is not only relevant for future stem cell therapy, but may also allow the preclinical testing of new drugs or combinations that are optimally suited for an individual patient.

This article is part of a Directed Issue entitled: Cystic Fibrosis: From o-mics to cell biology, physiology, and therapeutic advances.

Contents

Abbreviations: CFTR, cystic fibrosis transmembrane conductance regulator; rAAV, recombinant adeno-associated virus; NBD, nucleotide binding domain; MSD, membrane spanning domain; iPSC, induced pluripotent stem cells; CRC, conditionally reprogrammed cells; ROCK, Rho-kinase; ICM, intestinal current measurements; FIS, forskolin-induced swelling; PDE, phosphodiesterase; CAL, Golgi localized CFTR associated ligand; NHERF, Na+/H+ Exchanger Regulatory Factor; Fsk, forskolin; NMD, nonsense-mediated mRNA decay; PTCs, premature termination codons; PRs, proteostasis regulators; PCs, pharmacological chaperones; TMA, trimethylangelicin; HTS, high-throughput screening; ABPs, ATP binding pockets; WT, wild-type; FIS, forskolin-induced swelling; ALI, air–liquid interface; EMA, European Medicines Agency; FDA, Food & Drug Administration.

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http://dx.doi.org/10.1016/j.biocel.2014.02.008
1357-2725/

1. Introduction

Cystic fibrosis (CF) is a life-threatening autosomal recessive monogenetic disease caused by mutations in the CFTR gene, encoding a cyclic AMP- and cyclic GMP-regulated and ATP-gated chloride channel (Riordan, 2008). The impact of a defect in CFTR function differs among tissues and cell types (Antunovic et al., 2013). In sweat glands, the decreased reabsorption of sodium chloride by the water-impermeable ductal epithelium results in elevated sweat chloride, a hallmark of CF. In other epithelia, in particular the respiratory and intestinal epithelia as well as the biliary and pancreatic ducts, CFTR dysfunction causes a loss of chloride and bicarbonate secretion, resulting in cellular alkalinity and luminal acidification, impaired decondensation of discharged mucin granules by goblet cells, and defective mucus expansion (De Lisle and Borowitz, 2013; Greggio et al., 2013). The ensuing acidification and dehydration of the mucus layer leads to impaired mucociliary clearance and bacterial killing by epithelial defensins (Pezzulo et al., 2012); this predisposes to recurrent infection, inflammation, mucus plugging and luminal obstruction. Loss of CFTR function in monocytes and macrophages, by impairing phagocytosis and intracellular killing of *Pseudomonas aeruginosa*, contributes to the enhanced susceptibility to infection in patients with CF (Bonfield et al., 2012; Sorio et al., 2011; Van de Weert-van Leeuwen et al., 2013).

When CF was first described in 1938, the predicted survival age of a CF patient was only 6 months. For patients born in the 1990's median survival is now predicted to exceed 40 years (Wilschanski, 2013). This impressive gain in life expectancy has resulted largely from advances in early diagnosis and symptomatic treatment of end-organ pathologies based on vast improvements in nutrition, control of airway infections, and physiotherapy (see Fig. 1 for an overview of CF symptomatic treatment). Understandably the discovery of the disease-causing CFTR gene in 1989 created new hope for a curative treatment targeting the basic defect rather than treating CF disease manifestations (Clancy and Jain, 2012). The most obvious approach, viral or non-viral gene therapy, would potentially be of benefit to all patients with CF, independent of their genotype. So far however CFTR gene addition or gene replacement, despite promising advances, has not translated into clinical benefits despite more than 20 clinical trials, mainly due to a low expression of the CFTR transgene, inflammatory responses to viral proteins, the development of a humoral immune response preventing successful readministration, and the risk of insertional mutagenesis in case of integrating viral vectors. In contrast, considerable progress has been made in the development of tailored CFTR pharmacotherapy for specific CFTR mutations, and the design of better *in vitro* preclinical assays that allow the selection of the most effective therapeutic approaches on an individual basis, *i.e.* personalized medicine.

2. Mutation-specific therapies

Nearly 2000 mutations in the CFTR gene have been identified that can be subdivided in 6 different classes based on their phenotypic consequences (Fig. 2) (Derichs, 2013; Rogan et al., 2011). Class I mutations cause defects in full-length protein synthesis due to premature truncations or nonsense alleles, or to severe splicing defects; class II mutations cause folding defects and premature proteasomal degradation, class III shows normal trafficking to the plasma membrane but defective channel gating, class IV results in an impaired channel conductance, class V causes a reduced number of CFTR transcripts, and class VI is characterized by a reduced protein stability and increased turnover of CFTR at the cell surface. The first three mutation classes are associated with a nearly complete loss of CFTR channel function and are considered severe mutations, whereas mutations in class IV-VI may allow residual CFTR function and are associated with a milder phenotype. F508del, the most common mutation with an allelic frequency of around 90% worldwide, has mixed properties of class II, III and VI and is therefore most

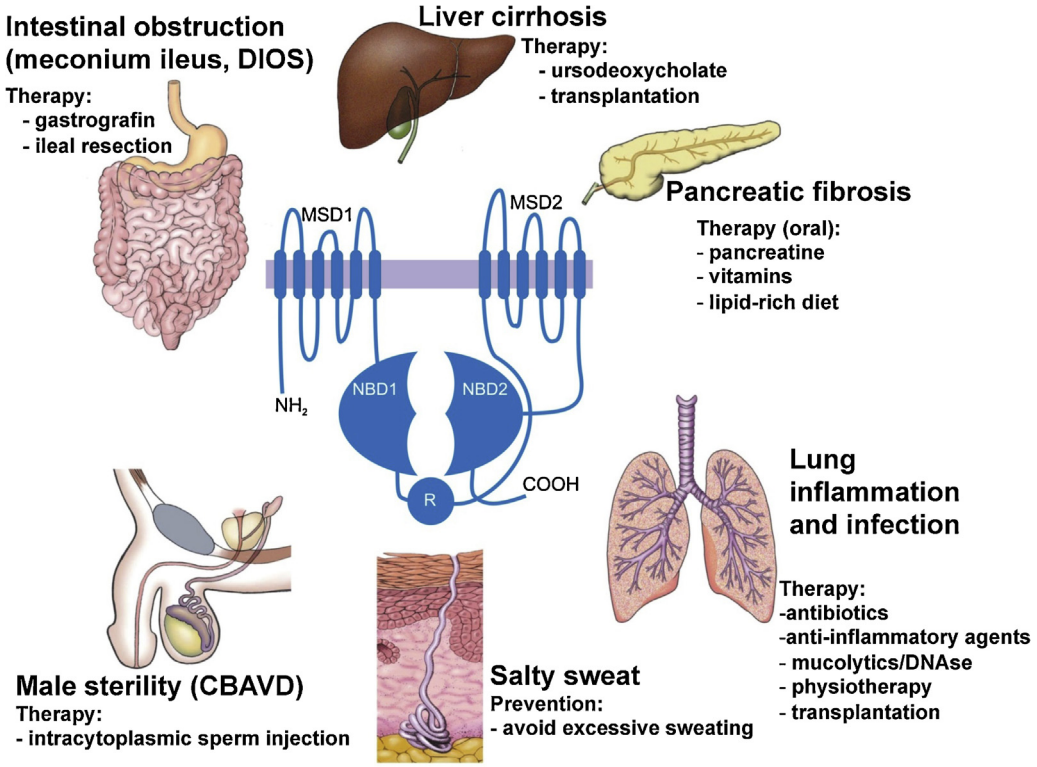

Fig. 1. Overview of current symptomatic treatments of CF. Inset: CFTR domain structure. MSD, membrane spanning domain; NBD, nucleotide binding domain; R, regulatory domain.

Please cite this article in press as: Ikpa PT, et al. Cystic fibrosis: Toward personalized therapies. Int J Biochem Cell Biol (2014), http://dx.doi.org/10.1016/j.biocel.2014.02.008