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Review

CFTR Protein Repair Therapy in Cystic Fibrosis☆

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ABSTRACT

Cystic fibrosis is a single gene, autosomal recessive disorder, in which more than 1900 mutations grouped into 6 classes have been described. It is an example a disease that could be well placed to benefit from personalized medicine. There are currently 2 very different approaches that aim to correct the basic defect: gene therapy, aimed at correcting the genetic alteration, and therapy aimed at correcting the defect in the CFTR protein. The latter is beginning to show promising results, with several molecules under development. Ataluren (PTC124) is a molecule designed to make the ribosomes become less sensitive to the premature stop codons responsible for class I mutations. Lumacaftor (VX-809) is a CFTR corrector directed at class II mutations, among which Phe508del is the most frequent, with encouraging results. Ivacaftor (VX-770) is a potentiator, the only one marketed to date, which has shown good efficacy for the class III mutation Gly551Asp in children over the age of 6 and adults. These drugs, or a combination of them, are currently undergoing various clinical trials for other less common genetic mutations. In the last 5 years, CFTR has been designated as a therapeutic target. Ivacaftor is the first drug to treat the basic defect in cystic fibrosis, but only provides a response in a small number of patients. New drugs capable of restoring the CFTR protein damaged by the most common mutations are required.

Tratamientos reparadores de la proteína CFTR en la fibrosis quística

Palabras clave:
Aatluren
Fármaco corrector
Fármaco modulador
Fármaco potenciador
Proteína reguladora de la conductabilidad transmembrana de la fibrosis quística
Ivacaftor
Lumacaftor

RESUMEN

La fibrosis quística es una enfermedad autosómica recesiva monogénica, de la que se han descrito ya más de 1.900 mutaciones agrupadas en 6 clases y que constituye un ejemplo de lo que podría ser una enfermedad bien situada para poder beneficiarse de la medicina personalizada. En la actualidad, 2 enfoques muy diferentes tienen por objetivo corregir el defecto básico: la terapia génica, dirigida a corregir la alteración genética, y la terapia encaminada a corregir el defecto a nivel de la proteína CFTR. Esta última comienza a dar resultados prometedores con diversas moléculas en desarrollo. Ataluren (PTC124) es una molécula diseñada para que los ribosomas se vuelvan menos sensibles a los codones de parada prematuros responsables de las mutaciones clase I. Lumacaftor (VX-809) es un fármaco corrector que está dirigido a mutaciones de clase II, entre las que figura la más frecuente (Phe508del), con prometedores resultados. Ivacaftor (VX-770) es un fármaco potenciador, el único comercializado hasta el momento, que ha demostrado una buena eficacia para la mutación de clase III, Gly551Asp, en niños mayores de 6 años y adultos. Además, diversos ensayos están probando estos fármacos o la combinación de ellos para otras mutaciones genéticas menos frecuentes. En los últimos 5 años, la CFTR ha sido designado como una diana terapéutica. Ivacaftor es el primer fármaco que trata el defecto básico de la fibrosis quística, pero solo da respuesta a un escaso porcentaje de los pacientes. Se precisan nuevos fármacos capaces de restaurar la proteína CFTR causada por mutaciones más comunes.

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Introduction

The completion of the human genome project was a relevant milestone for medical knowledge, providing the information necessary for understanding the unique characteristics of each individual.[1] The logical consequence of this knowledge would be to be able to apply specific diagnostic tests and treatments to each patient based on their individual genetic information. This new form of medical care is called personalized medicine.[2] However, despite the great progress that has led to the knowledge of the human genome, its translation into diagnostic and personalized treatments has been less than expected. At present, steps are being in this direction with two major initiatives: systems biology[3] and pharmacogenetics.[4] The ultimate goal of these initiatives is to develop a medical practice customized to the characteristics of each individual that can predict the onset or course of a particular disease, allow appropriate prevention strategies to be established and, finally, enable the patient to take part in the decision making. This has been called P4 medicine.[5]

Cystic fibrosis (CF) remains the most common and lethal genetic disease among Caucasians. It occurs at a rate of 1 in 2500–6000 newborns, depending on the region and ethnic origin, and in a proportion of healthy carriers, varying between 1:20 and 37.[6] In Spain, thanks to the progressive introduction of neonatal screening programs in the different communities, a lower incidence of CF is now being seen than was previously estimated in 2009, *i.e.*, 1/4430 live births in Galicia, 1/4339 in Castile-Leon, 1/5376 in Murcia, 1/5840 in Catalonia, and 1/6602 in the Balearic Islands.[7] It is estimated that there are 70 000 CF sufferers worldwide.[8] The disease is caused by mutations in the gene encoding the regulatory protein cystic fibrosis transmembrane conductance regulator (CFTR), a chloride channel involved in the release of adenosine triphosphate and regulation of other ion transport channels. This protein is expressed in respiratory epithelial cells, pancreas, biliary tract, sweat glands and genitourinary system. Its alteration leads to an abnormality in ion transport, so that patients produce thick, sticky mucus that clogs the ducts of the organ where it is located and so the alteration presents multisystemic effects that determine the wide range of clinical manifestations of CF. Despite major advances in the treatment of CF that have resulted in longer survival (present median is estimated in 37.5 years),[9] there is still a long way to go to ensure that patients with CF have a quantity and quality of life similar to that of subjects without the disease. In this context, new treatments to decrease morbidity and increase survival are necessary.

CF is an example of a disease well-positioned to take advantage of personalized medicine. On one hand, it is a monogenic disease, caused by the mutations in a specific gene. The pathophysiology of the entity is well characterized and the therapeutic targets are clear. Furthermore, diagnosis of the disease requires genetic testing for the identification of the disease type, so the exact genetic defect is determined in each case.[10]

At present, two very different approaches are targeted at correcting the basic defect: gene therapy, aimed at correcting the genetic alteration, and molecule therapy, aimed at correcting the functional defect at the protein level. The focus of gene therapy is the introduction of normal gene copies in the airways of CF patients. It involves the insertion of a recombinant viral vector, the DNA of which has been extracted and replaced by the new therapeutic DNA. The viral vector serves as a vehicle for inserting the new DNA into the target cell. Various types of viruses, such as adenovirus or lentivirus, have been used to date. Furthermore, non-viral particles, such as nanoparticles capable of inserting DNA, have also been developed.[11] However, the results so far have been poor, because the duration of expression of the introduced gene was short with both types of vectors.[12] The UK Gene Therapy Consortium is developing a phase II clinical trial to evaluate the clinical effectiveness of an optimized plasmidic/liposomal DNA vector.[13] The recruitment target is 130 patients and results are expected in 2014 (NCT01621867).[14]

On the other hand, therapy directed at restoring the function of the CFTR protein has been more successful. In recent years, results are beginning to come through on drugs that act directly on the CFTR protein. In fact, in January 2012, the first drug for correcting Gly551Asp mutation defects was marketed in the USA. In the following sections we will review the available information on the progress of personalized medicine for CF and available treatments aimed at correcting the defect causing the disease at the protein level. In this review, the nomenclature used for the description of CFTR gene mutations developed by the Human Genome Variation Society[15] will be used.

Mutations and Protein Defect

CF is an autosomal recessive hereditary disease, so the mutation must be present in both copies of the CFTR gene to be affected. To date, over 1900 CFTR gene mutations associated with the disease have been identified in the coding sequence, messenger RNA or other elements. Mutations in the CFTR gene are available for consultation in the Cystic Fibrosis Mutation Database.[16] The first mutation described, and the most common worldwide, is Phe508del, but there are other specific mutations with varying frequency among different ethnic groups. In Spain, the average frequency of Phe508del mutation is between 50% and 60% of all of the studied chromosomes, the second most frequent is Gly542X with 4%–8%, followed by Asn1303Lys in 2%–4% of cases. The mutations described to date are classified into six types or classes according to the mechanism causing the disease.[17] These types of mutations are summarized in Fig. 1. Class I mutations lead to a premature stop codon in the messenger RNA which prevents translation of the complete protein. Thus, the protein produced is short and nonfunctioning. Class II mutations encode a structurally abnormal and misfolded protein that is removed by the endoplasmic reticulum before reaching the cell surface. The most common mutation in CF, Phe508del, belongs to this group. In the case of mutations in classes III to VI, proteins reach the cell surface, but do not function properly. Class III mutations cause a decreased channel activation, so channels remain closed. Class IV mutations cause a decrease in ion conductance through the channel. Class V mutations encode minor proteins resulting in a reduced amount of CFTR in the cell surface, so that a certain function occurs, but at a reduced level. Finally, class VI mutations lead to a shortened half-life due to protein instability and can also damage the regulation of neighboring CFTR channels in the cell surface.

CFTR Modulators

Three main classes have been identified in the development of drugs for repairing CFTR protein.[11] The first group are premature stop codon suppressors (class I mutations). These drugs prevent identification of this premature stop codon, so that protein synthesis can continue until completion. The second group are the CFTR correctors. These compounds are designed to correct defects in the transport of folded protein (class II mutations) to the cell membrane, where it may be able to function almost normally. The third group consists of the so-called CFTR potentiators. These are drugs designed to target the CFTR protein on the cell surface in order to improve its function. Thus, these potentiators can act on class III, IV, V and VI mutations. Currently, numerous molecules using these different mechanisms are under investigation, one of which has already reached the market: Ivacaftor (VX-770) is a CFTR potentiator approved in the USA in January 2012 for the treatment