European Cystic Fibrosis Society

Journal of Cystic Fibrosis
The Official Journal of the European Cystic Fibrosis Society

Cystic Fibrosis Research News

Title:
Lumacaftor-rescued F508del-CFTR has a modified bicarbonate permeability

Authors:
Loretta Ferrera[1], Debora Baroni[2] and Oscar Moran[2]

Affiliations:
[1]Istituto Giannina Gaslini, U.O.C. Genetica Medica, Genova, Italy
[2]CNR, Istituto di Biofisica, Genova, Italy

What was your research question?
The cystic fibrosis transmembrane regulator (CFTR) protein is a cellular channel permeable to small particles charged negatively as chloride and bicarbonate. We studied if lumacaftor, a substance approved in CF human disease, changes the CFTR permeabilty in cells lines with deletion of the amino acid phenylalanine at position 508.

Why is this important?
Deletion of the amino acid phenylalanine at position 508 is the most frequent mutation in CFTR causing CF and the most common cause of illness and death in CF is lung disease, which is characterised by infection, inflammation and airway damage that leads to a lack of oxygen getting into the blood. It is caused by modifications of the fluid that hydrates the airways. The equilibrium of the epithelium surface is finely controlled by the composition of this liquid. The rescue of the mutant CFTR without preserving correct ionic selectivity properties could compromise airways liquid composition and therefore the lung function.

What did you do?
The role of CFTR in membranes covering internal organs is to transport not only chloride (salt), but also bicarbonate, which is important for regulating the acidity of the fluid on the airway surfaces, which, in turn, determines how sticky the mucus is. We focused our attention on how bicarbonate moves through the cell walls after treatment with lumacaftor.in order to examine if mutated CFTR retains the same relative permeability for chloride and bicarbonate as that reported in normal CFTR.

What did you find?
We found that compared with the normal CFTR, the F508del-CFTR treated with lumacaftor shows a different permeability for chloride and bicarbonate. This suggests a different

composition of the airways liquid also in CF patients treated with lumacaftor and in could explain the limited clinical outcome.

What does this mean and reasons for caution?

Since the transport properties of a membrane channel is defined by its correct three-dimensional frame in the cell, the difference between normal and mutated CFTR suggests that the rescue of the F508del-CFTR by lumacaftor probably results in a protein with an altered structure of the away where chloride and bicarbonate go through. This finding is consistent with other structural data (Baroni et al Cell Mol Life Sci 72, 1363–75, 2015).

What's next?

Researchers need to identify other "corrective" compounds that work together with lumacaftor to make sure the mutated F508del protein is folded correctly.

Original manuscript citation in PubMed

https://www.ncbi.nlm.nih.gov/pubmed/?term=Lumacaftor-rescued+F508del-CFTR+has+a+modified+bicarbonate+permeability