

Cystic Fibrosis Research News

Title:

Rescue by elxacaftor-tezacaftor-ivacaftor of the G1244E cystic fibrosis mutation's stability and gating defects are dependent on cell background

Lay Title:

Study of how the G1244E cystic fibrosis mutation modifies the CFTR function and response to available CFTR modulators

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What was your research question?

Cystic fibrosis (CF) is caused by mutations in the gene that produces the cystic fibrosis transmembrane conductance regulator (CFTR) protein causing various types of defects that lead to loss of function of the CFTR protein. These alterations may be rescued by drugs known as 'correctors' - small molecules which bind to the CFTR protein and improve its shape, and 'potentiators' - which work by hold the 'gate' of the CFTR channel open so chloride can flow through the cell membrane, therefore increasing CFTR activity.

Why is this important?

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The G1244E mutation causes a severe 'gating' defect (the ion channel won't open or close) that it is not completely rescued by the ivacaftor (a potentiator) but requires the use of a second compound (a co-potentiator). Recently, it has been proposed that the corrector elxacaftor may act also as a co-potentiator. We aimed to study the mechanism by which modulators rescue G1244E-CFTR to optimize therapies for people with CF with this mutation.

What did you do?

We studied how the G1244E mutation alters the function of CFTR. Firstly, we used cells derived from the internal surface of the nostrils from people with CF (pwCF), recovered by gentle brushing. These cells allow to study the activity of CFTR and the effect of modulators in the proper, native cellular context. Nasal epithelial cells are cultured to assume the characteristics they have within the body. The effect of the modulators is tested on these cells and studied at the functional, molecular and biochemical level. Secondly, we studied the G1244E CFTR mutation in cells usually used in laboratory and widely applied in CF research. We used different type of cells because every cell type has unique characteristics. Thus, it is important to study the effect of the G1244E CFTR mutation in all these different contexts.

What did you find?

Our studies demonstrate the G1244E CFTR mutation alters the CFTR function differently in the different cells including those derived from the nose of pwCF. This implies that also the response to CFTR modulators, differs in the various cell types. In the laboratory cell lines, elxacaftor mainly acted on G1244E-CFTR like a potentiator, with a benefit for the CFTR activity. On the contrary, in the nasal cells from pwCF, elxacaftor did not act as a potentiator, but it increased the quantity of mature CFTR possibly by allowing the protein to stay for a prolonged time on the cell membrane, which is beneficial for its function.

What does this mean and reasons for caution?

Our study highlights the importance of studying the effect of the CFTR mutations in different types of cells. In particular, the use of cells derived from pwCF, such as those collected from the nose, helped us to explain the exact way in which elxacaftor works on a specific CFTR mutation. Our work demonstrates the efficacy of elxacaftor-based therapies for pwCF with the G1244E mutation. However, these results also draw attention to the need for the development of new potentiators having different mechanisms with respect to ivacaftor for mutants displaying severe activity defect to obtain optimal rescue of CFTR function, as in the case of G1244E.



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What's next?

Our work suggests that nasal cells derived from people with CF are one of the best models to study the effect of CFTR mutations, as they keep the biological features of each single person. Since they replicate in a laboratory dish all the features of the CF people's airways, these cells are also extremely important to investigate and predict the individual cell response to available CFTR modulating drugs.

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