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Cystic Fibrosis Research News

Title:
A MUTATIONAL APPROACH TO DISSECT THE FUNCTIONAL ROLE OF THE PUTATIVE CFTR "PTM-CODE"

Lay Title:
The role of the "PTM-CODE" in restoring F50del-CFTR functionality

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What was your research question?
It is well known that after it is made in the cell, the CFTR protein undergoes the binding of different chemical entities to specific amino acids of the protein, known as post-translational modifications (PTMs). We wanted to know if it is possible to restore the function and the location in the cell membrane of F508del-CFTR by adjusting PTMs.

Why is this important?
It was reported that some modifications in a specific portion of the CFTR protein (dubbed PTM-code) were associated with the fully functioning version of CFTR, which can reach the cell membrane and work properly. Alternatively, a different pattern was typical of the faulty channel. Therefore, it might be possible to adjust these PTMs to restore the mutated forms of CFTR.

What did you do?
Our investigation aimed to decipher if the PTM-code contributes to restoring CFTR. By using a mutational approach and preventing the addition of these functional groups to the F508del-CFTR one by one, we wanted to see if the generation of the PTM-code is important for the recovery of F508del-CFTR. So we tested the efficiency of elexacaftor and tezacaftor (included in triple combination therapy known as Trikafta or Kaftrio) in restoring the functionality of F508del-CFTR in which the generation of the PTM-code was completely inhibited.

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What did you find?

Unfortunately, our data showed that the PTM-code was not needed to restore the functional F508del-CFTR; indeed, eliminating it did not influence how well F508del-CFTR was restored after the treatment with elexacaftor and tezacaftor.

What does this mean and reasons for caution?

Regulating the PTM-code would not be essential for treatment. However, to date we have focused our attention on a small group of post-translational modifications, while there are about a hundred of CFTR modifications currently known. For most of them, their role in the functioning of the CFTR channel is still to be resolved.

What's next?

Understanding the role of these orphan modifications and identifying the enzymes that generate them could be of great importance for the restoration not only of F508del-CFTR but also of other mutations which impair trafficking of the CFTR protein.

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