Cystic Fibrosis Research News

Title:
Rescue of CFTR NBD2 mutants N1303K and S1235R is influenced by the functioning of the autophagosome

Authors:
Qiangni Liu, Inna Sabirzhanova, Murali K. Yanda, Emily A.S. Bergbower, Clément Boinot, William B. Guggino, Liudmila Cebotaru

Affiliations:
Departments of Medicine and Physiology, Johns Hopkins University, Baltimore, MD, USA

What was your research question?
Many changes in the DNA code for the CFTR gene (mutations) can cause the CFTR channel protein to be defective, which is the cause of cystic fibrosis (CF). Although there seems to be continued success with a new therapy to treat the ΔF508-CFTR mutation, the most common mutation, question arises as to whether therapies can be developed for other CFTR mutations. We focused on two mutations called N1303K-CFTR and S1235R-CFTR.

Why is this important?
The ΔF508-CFTR mutation causes the CFTR channel to be misfolded and as a result it is disposed of by the cell, breaking it down into small pieces. This mutation was once thought to be uncorrectable, but a drug called lumacaftor was found to prevent CFTR from being broken down into small pieces. This allows the CFTR channel to move to the cell surface where another drug ivacaftor, can help it open and perform its function. This combination (known as Orkambi) allows partial restoration of ΔF508-CFTR trafficking and function. Although there seems to be continued success with ΔF508-CFTR, the question arises as to whether therapies can be developed for other CFTR mutations.

What did you do?
We previously studied these two mutants and found that both have characteristics which are in some ways similar to ΔF508-CFTR but in other ways are unique. We study in more detail as to how CFTR with these mutations are degraded and if they can be rescued, particularly for N1303K-CFTR which causes severe CF disease. In a recent study, we found that a different pathway is involved in removing N1303K-CFTR. This pathway is called autophagy or “self
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eating” and is a process that clears the cell of components that cannot be degraded by simple digestion but instead “swallows” defective proteins as a whole piece.

**What did you find?**
We found that N1303K-CFTR associates with several molecules which are typically involved with degradation. However, instead of being degraded, N1303K-CFTR stalls the self-eating process and remains as a damaged protein. We found that treating N1303K-CFTR and S1235R-CFTR with combinations of chemical corrector compounds can release them from the process of “self-eating” and as a result, CFTR function is improved.

**What does this mean and reasons for caution?**
The challenge will be to develop our findings into therapeutically effective combined corrector cocktails that will be effective in treating patients bearing these CFTR mutations. Our data show that combinations of compounds that rescue ΔF508-CFTR, may be effective in rescuing N1303K-CFTR.

**What’s next?**
A further challenge is to develop effective treatment for mutants such as N1303K-CFTR that engage the cell in ways inherently different from ΔF508-CFTR. Treatments designed more specifically to rescue N1303K may be more efficient than using those already developed to treat ΔF508-CFTR. Our studies provide a path forward for the development of these treatments.

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