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Title:

Evaluation of a systems biology approach to identify pharmacological correctors of the mutant CFTR chloride channel

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What was your research question?

We were interested in studying ways to improve the performance of drugs that correct the function of CFTR protein carrying the F508del mutation (the most common mutation among cystic fibrosis patients).

Why is this important?

When CFTR protein has the F508del mutation, it cannot assume its normal 3-dimensional structure. Because of this, the protein gets trapped inside the cell and is not delivered to the cell surface. The defects caused by F508del can be mitigated using chemical compounds called correctors. However, the correctors identified so far, such as the drug VX-809, only partially correct the mutant CFTR protein. New and more effective treatments need to be identified. Such treatments will probably be based on combinations of correctors that work in complimentary ways, such that together they can produce a more effective restoration of CFTR function than any one drug working alone.

What did you do?

It is known that growing cells at a temperature lower than normal human body temperature increases the effect of current corrector drugs such as VX-809, but exactly how the lower temperature increases the performance of the drug is not known. Growing cells at a cooler temperature has widespread effects on the cells in terms of which genes are turned on and off (and to what degree). We thought that a subset of these effects on the cells genes might be responsible for the increase in performance of VX-809. We used sophisticated software to compare the set of genes that are turned on and off by cooler temperature to a public database that contains information on which genes are turned on and off by thousands of

known drugs. In this way, we obtained a list of drugs whose effects on the cell's gene pattern were similar, at least in part, to that of low temperature.

What did you find?

We tested the drugs identified using the software program on cells grown in the laboratory that produced CFTR protein with the F508del mutation. We found that a group of steroids, (that include mometasone, budesonide, and fluticasone), could restore function to the mutation CFTR protein, particularly when they were used in combination with VX-809. Unfortunately, when we tested the drugs on cells that we obtained directly from cystic fibrosis patients, they were ineffective on CFTR and actually had an unexpected side effect that might further worsen the dehydration in the airways of cystic fibrosis patients.

What does this mean and reasons for caution?

There are two possible ways in which low temperature might restore function to mutant CFTR protein. The first is through a change in the pattern of other genes that are on or off, which could in turn help mutant CFTR to achieve a correct 3-dimensional structure. The second mechanism is of the cold temperature that itself somehow helps mutant CFTR protein to achieve a correct 3-dimensional structure. Because we were unable to find a drug that could recapitulate the effect of cold temperature and restore function to mutant CFTR, we now think that this approach to restoring function to the F508del mutant CFTR protein is too difficult to be practical, and that drugs directly targeting CFTR are more likely to be successful.

What's next?

It is important to better understand the mechanisms that are involved in the restoration of function to mutant CFTR by low temperature. Ultimately, it may be possible to find a drug that can mimic the beneficial effects of cold temperature. Such a drug may be useful in overcoming the negative effects caused by F508del mutation.

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