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Title:

AMPLIFIERS CO-TRANSLATIONALLY ENHANCE CFTR BIOSYNTHESIS VIA PCBP1-MEDIATED REGULATION OF CFTR mRNA

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What was your research question?

We wanted to determine how amplifiers, which are a novel class of CFTR modulator, work to increase CFTR levels.

Why is this important?

The studies described in our research point to the mechanism for how amplifiers work. Amplifiers are CFTR modulators that increase the levels of CFTR protein, providing more for other types of CFTR modulator to work on. Nesolicaftor, a first-in-class CFTR amplifier, has been shown in clinical studies to synergize with the corrector posenacaftor and the potentiator dirocaftor to provide improved lung function and to reduce sweat chloride concentration in CF patients. An understanding of how amplifiers make more CFTR is important as a first step towards finding and developing even better therapeutics that act in this way.

What did you do?

We first looked at how amplifiers are increasing the amount of CFTR in cells. CFTR gets made through a process called “translation”. We tested whether translation was important for the

amplifier to work, and whether the amplifier specifically increases CFTR translation. We then looked for what proteins present in lung and liver cells bind to amplifier and found that a protein called PCBP1 binds to it. PCBP1 is known to affect translation. Lastly, we studied the relationship between PCBP1, CFTR and the amplifier to understand how amplifier leads to an increase in CFTR translation in the cell. R.

What did you find?

In cells, amplifier increases the message coding for CFTR, which leads to an increase in CFTR protein. If normal translation is blocked, so is the increase, suggesting that amplifier acts during CFTR protein translation. We found that amplifier binds PCBP1, a protein that interacts with messages and regulates their translation into proteins. Our experiments demonstrated that amplifier binds even better to PCBP1 in the presence of CFTR message, and that response to amplifiers, namely the increase in CFTR, can be prevented by changing parts of the CFTR message that are important for binding to PCBP1.

What does this mean and reasons for caution?

We now have a much better understanding of how amplifiers increase the levels of CFTR and contribute to higher CFTR activity when combined with other CFTR modulators. We have also identified a new step in how CFTR is made and this can possibly be targeted by new drugs to find new therapies in CF. This knowledge can potentially guide ways to design and develop improved amplifiers. Our findings are the first step in pursuing such improvements. PCBP1 does many jobs in cells, and the ability of amplifiers to increase CFTR through PCBP1 may be unique to this class of modulator.

What's next?

We will use this new knowledge to further improve and optimize amplifiers as therapeutics. We will also further study PCBP1 to look for different ways we can approach its effect on CFTR as a new therapeutic approach for CF.

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