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Title:

RESCUE OF CHLORIDE AND BICARBONATE TRANSPORT BY ELEXACAFTOR-IVACAFTOR-TEZACAFTOR IN ORGANOID-DERIVED CF INTESTINAL AND CHOLANGIOCYTE MONOLAYERS

Lay Title:

Restoration of the chloride and bicarbonate (soda) transport function in cystic fibrosis by Kaftrio

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What was your research question?

Is Kaftrio able to rescue both the chloride and bicarbonate ("soda") transport function of the CFTR channel in two major CF-affected organs, the intestine and the liver?

Why is this important?

The CFTR protein that is mutated in CF not only serves as a chloride channel but also transports bicarbonate, the main component of soda. Many studies have shown that CFTR modulator drugs, including Kaftrio, rescue CFTR chloride transport. However, their effect on bicarbonate transport has been poorly investigated, even though the loss of bicarbonate secretion plays a key role in the CF-typical accumulation of viscous mucus in the airways and the gut.

What did you do?

We collected small tissue samples (biopsies) from the small intestine and the liver of CF subjects carrying the most common CFTR mutation, F508del, and used them to generate intestinal and bile duct organoids (mini-organs). These organoids were grown as epithelial

sheets on filters, mounted in so-called Ussing chambers, and exposed to chloride- or bicarbonate-rich fluids. This allowed us to measure chloride and bicarbonate transport across these epithelia separately, and to monitor restoration of transport following treatment with elexacaftor, ivacaftor and tezacaftor (ELX/IVA/TEZ), the key components of Kaftrio.

What did you find?

ELX/IVA/TEZ strongly enhanced both chloride and bicarbonate transport in the CF intestinal organoids, reaching 50% of non-CF values. Surprisingly, in the biliary organoids, the modulator cocktail effectively rescued chloride transport, but failed to restore bicarbonate transport. However, this defect is likely to be compensated for by two other bicarbonate transporters we found to be highly expressed in the biliary organoids, i.e. a non-CFTR channel and a chloride/bicarbonate exchanger. Indeed, we found that this alternative channel transports bicarbonate in CF as well as in non-CF organoids. Moreover, it is likely that CFTR modulator-enhanced chloride transport will boost bicarbonate secretion via the exchanger.

What does this mean and reasons for caution?

Our study predicts that the inability of ELX/IVA/TEZ to rescue bicarbonate transport in the CF liver is compensated for by its remarkable capacity to stimulate chloride secretion up to levels that exceed chloride secretion in non-CF organoids. This chloride may re-enter the cell in exchange for bicarbonate, providing a compensatory mechanism to restore bicarbonate secretion in the CF bile ducts. Direct proof of this model awaits the development of more sensitive methods to monitor secretion of bicarbonate by the exchanger, which escapes detection in the electrical current measurements used in this study.

What's next?

Our ambition is to extend this study to organoids from other CF-affected epithelia (airways, pancreas), to examine the effect of ELX/IVA/TEZ on other CFTR mutations, and to test bicarbonate rescue by other CFTR modulators, including new drugs emerging from the therapeutic pipeline. We are especially interested to learn whether some of these drugs restore bicarbonate transport equally well or even better than chloride transport.

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