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Cystic Fibrosis Research News

Title:

CFTR rescue with VX-809 and VX-770 favors the repair of primary airway epithelial cell cultures from patients with class II mutations in the presence of *Pseudomonas aeruginosa* exoproducts

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What was your research question?

Our work previously unveiled that molecules called correctors were not only able to rescue the cystic fibrosis transmembrane conductance regulator (CFTR) protein but also improved the repair ability of the injured airway lining (epithelium). Our goal was now to evaluate the efficiency of the clinical relevant combination (Orkambi) of the CFTR corrector VX-809 and potentiator VX-770 on epithelial repair, in infectious conditions.

Why is this important?

Respiratory failure due to progressive lung damage remains the leading cause of death in people with cystic fibrosis (CF). Unfortunately, our data revealed that injuries of the respiratory epithelium from CF patients heal more slowly than in a healthy epithelium. This phenomenon is most likely due to the CFTR dysfunction and infections, especially with *Pseudomonas aeruginosa* bacteria, frequently seen in CF lungs. Moreover, some evidence, including from our laboratory, indicate that these bacteria alter the efficiency of CFTR correctors. These observations may explain, at least in part, the limited efficacy of treatments with CFTR correctors to restore the function of damaged lungs in people with chronic infections.

What did you do?

We are using cutting-edge protocols established in our laboratory and airway tissues collected from non-CF and CF patients (carrying the most frequent mutation, F508del, or other mutations from the same class) during nasal surgery or lung transplantation. With these protocols, we were able to isolate epithelial cells and then to re-create airway epithelia mimicking the main characteristics of this tissue observed in the lung. The ability to repair after injury was then compared after treatments with VX-

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809 alone or in combination with VX-770, in the presence or absence of harmful products from *Pseudomonas aeruginosa* bacteria.

What did you find?

Our study revealed that the Orkambi combination (VX-809 and VX-770) had a higher beneficial effect on airway epithelial repair than the corrector (VX-809) alone, in the absence of infection. This treatment with Orkambi was effective not only on tissues from patients homozygous for the F508del mutation but also from heterozygous patients carrying F508del and another mutation from the same category (class II, N1303K or I507del). Although exposure to products from *Pseudomonas aeruginosa* bacteria dampened epithelial repair, a slight but significant improvement was observed after Orkambi treatment, despite this infectious condition.

What does this mean and reasons for caution?

Our study first highlighted that despite variability among patients, Orkamki treatment not only allowed partial rescue of CFTR but also favored the repair of airway epithelia from CF patients with different class II mutations. However, the relatively modest improvement observed in the presence of infection, may explain, at least in part, the limited beneficial effect of Orkambi on the lung function of people with CF, especially those with severe lung damage and bacterial infections. Complementary approaches are thus needed to further improve CFTR rescue and the restoration of lung tissue and function in people with CF.

What's next?

We are investigating the identity of harmful bacterial products and developing strategies to counteract their negative effect to enhance the treatment effectiveness.
Our goal is also to identify the most efficient combinations of molecules to restore lung tissue and function, even in people with infections, who are carrying various types of mutations.

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