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Commentary

Predicting CFTR activity with front-runner cystic fibrosis drugs

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The past two decades have seen most research efforts targeted at correcting the ion transport deficiency of cystic fibrosis (CF), highlighting the required promotion and development of new drugs to tackle CF (Becq et al., 2011; Boyle and De Boeck, 2013; Riordan, 2008). The polyexocrinopathy genetic disease CF is caused by one of the 2000 documented mutations in the cystic fibrosis transmembrane conductance regulator gene (*CFTR*, OMIM #602421) among them the deletion F508 (F508del-CFTR) is the most common and severe CF mutation (Boyle and De Boeck, 2013; Riordan, 2008). F508del causes CFTR misfolding/instability leading to defective protein biosynthesis, reduced plasma membrane residence and altered channel gating (Riordan, 2008; Becq, 2010). Whereas it remains unclear whether current small molecules targeting F508del-CFTR will have therapeutic benefit, the wind is nevertheless changing for CF patients who are still awaiting a curative treatment. Indeed, new medications with orphan drug status are, for some, rapidly progressing in clinical trials (Becq et al., 2011), among them the F508del-CFTR corrector lumacaftor (VX-809) (Van Goor et al., 2011). Acceleration of drug development has been clearly encouraged by the recent successful marketing of Kalydeco®, the first personalized medication for CF patients directly targeting mutated CFTR proteins (Ramsey et al., 2011).

The CF mutations can be classified into six classes (Welsh and Smith, 1993) helping research to being directed toward mutation-specific therapeutic agents. The most severe cases of CF belong to classes I, II and III, where little or no cAMP-dependent CFTR-mediated chloride ion transport is observed in epithelia expressing CFTR mutants. Mutations that have not been fully analyzed yet will be characterized as mutations of unknown clinical significance. Despite the fact that F508del-CFTR is the main target for drug development in CF (Becq et al., 2011), categorizing about 2000 individual mutations identified so far in patients worldwide would be a tough job while still remaining an important challenge. It is also necessary to understand whether the mutation themselves can cause CF or not, or a CF-related disease (e.g., congenital bilateral absence of the vas deferens or CBAVD, or pancreatitis). For CF patients with a heterozygous genotype, it is also important to understand whether carrying a CF-causing mutation actually results in CF or not.

In theory, the goal for such a classification is to predict the phenotype of a CF patient according to his/her genotype, but in practice this critically depends on our ability to functionally characterize the mutant CFTR. But, not all the CF mutations have been classified so far because the function of CFTR remains unknown for many of them. Equally important is the perspective, raising on the horizon, to propose a personalized medication according to the mutation(s) (Ikpa et al., 2014). Although controversial, predicting drug-induced response is indeed an attractive challenge that might well be added to (or even better replace) the therapeutic arsenal against the disease (Ikpa et al., 2014; Balfour-Lynn, 2014).

However, if we aimed to functionally characterize most CFTR mutants, then it is also important to determine how to measure CFTR activity with a rare mutation when testing corrector candidates and how to take into consideration the genotype of the epithelial CF model cells. In other words, if we want to personalize future treatments for CF patients, would it be necessary to systematically study most CF-related mutations or group of mutations during pre-clinical phase, and if the answer is yes, then how? In this issue of *EBioMedicine*, a research group led by Margarida Amaral (Awatade et al., 2015) described a method to functionally characterize the activity of CFTR in human primary lung cells by measuring the forskolin plus genistein-inducible equivalent short-circuit current in perfused open-circuit Ussing chamber (forskolin and genistein being pharmacological stimulators of CFTR). This study provides important information. The authors evaluated and compared the efficacy of correctors lumacaftor (VX-809) and its analogue C18 on epithelial cell preparations obtained from donors with different CF genotypes — homozygous for F508del, A561E or heterozygous N1303K/G542X, F508del/G542X, F508del/Y1092X. This strategy allowed them to compare, using a robust functional assay, different CFTR mutations in their native cell environment. Although they observed great variability in VX-809 responses among patients, they were able to discriminate CFTR mutants positively responding to the correctors such as A561E and Y1092X and those that failed to respond, such as N1303K. They also compared the efficacy of the correctors and again found differences for a given mutation. In principle, the protocol used by Awatade et al. (2015). is simple and can be implemented in many research laboratories worldwide, but it is not a common practice to use human bronchial epithelial cells with different genotypes because such material is rare. It is usually a long process to obtain enough patient samples and enough epithelial cell quantities within the tissue sample to complete a study and collaboration between transplantation and research centers are generally complicated to set up. These results are thus telling us that not only might it be important to use human primary epithelial cells with various genotypes but it might equally be important to test several correctors for each CFTR mutant due to different mechanisms of action.

Therefore, whereas the study of Awatade et al. (2015) confirms the feasibility of exploring how CFTR might work with different mutations

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and with the best front-runner CF correctors, if the future for the disease is to tailor an appropriate pharmaceutical product, then it will require a great amount of effort to correlate drug effect with specific CF mutations.

Conflicts of interest

The author declares no conflicts of interest.

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