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Editorial

Tissue-Specific Biomarkers for Cystic Fibrosis Therapy: Conundrum or Opportunities?

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EDITORIAL

Cystic Fibrosis (CF) is a multisystem disease that arises from mutations in a single gene encoding a cAMP-activated anion channel known as the cystic fibrosis transmembrane conductance regulator (CFTR) [1]. While fixing the root cause through CFTR modulation is expected to completely reverse the multisystem symptoms, the efficacy of such an approach also depends on a number of other factors such as the age and genetic makeup of the patient, environment factors, and the stage of the disease a specific patient is in. The presence of over 2,000 mutations in the CFTR gene and their varied properties add an extra layer of complexity to the expression of symptoms and responses to pharmacological treatment.

Lung disease is the major cause of morbidity and mortality among CF patients, and lung functional test is the most important clinical criterion for assessment of treatment efficacy. An increase in percent predicted forced expiratory volume in 1 second (ppFEV1) and a reduction in the frequency of pulmonary exacerbation are key clinical indices for improved CF lung function. With the recent successful development of CFTR modulators [2-4], CFTR function-based, tissue-specific biomarkers have been incorporated into clinical trials as surrogate endpoints [5]. The hope is that such biomarkers will be both selective and sensitive, accelerating CF drug development.

Several such biomarkers have been used as surrogate outcome measures in recent clinical trials of CFTR modulators [5]. They include sweat test, nasal potential difference (NPD), and intestinal current measurement (ICM). Sweat test measures sweat chloride concentration. It reflects the capability of CFTR in sweat chloride resorption, and is the gold standard for definitive CF diagnosis. NPD reflects both sodium absorption and chloride secretion, *in vivo*, in the upper airway. ICM, on the other hand, is an *ex vivo* measure of transepithelial short-circuit current of rectal biopsy.

Based on clinimetric properties of these biomarkers, NPD demonstrates reliability, validity, and responsiveness to drug treatment; sweat test shows validity and responsiveness but not reliability; and ICM displays reliability but not validity or responsiveness [5]. Such inconsistency among the different biomarkers creates a conundrum when they are used as surrogate endpoints in clinical trials. While each biomarker is based on CFTR functionality, they are specific for three different tissues affected in CF. Chloride transport in the sweat gland provides the most direct assessment of CFTR activity uncomplicated by other pathophysiological changes in the tissue, and therefore provides good validity and responsiveness. In fact, sweat test will accurately reflect missed doses and therefore can be used as an internal control for patient compliance in clinical studies [6,7]. For the same reason, sweat test does not accurately reflect the complex pathophysiological changes in the lung, upon which the key clinical outcome relies. In contrast, NPD reflects the airway, the most important tissue for CF therapy, and therefore offers a more reliable readout on CFTR activity in the lungs. The different CF pathophysiology in the gut might explain the low validity and responsiveness of ICM.

Given the different degrees of alignment of various CFTR function-based, tissue-specific biomarkers with the lung function of CF patients, rather than unsuccessfully forcing these biomarkers into surrogate endpoints for CF lung function, we should seriously consider combinational use of these biomarkers in a tissue-dependent manner to provide a more complete and accurate picture of the multisystem symptoms of CF and their response to pharmacological treatment.

The CF sweat gland is among the CFTR-expressing organs that have the least clinical consequences and is uncomplicated with other local pathophysiological changes. Therefore, sweat test can be used as a highly reproducible measurement of CFTR function when CFTR modulators are used. In addition, it can serve an auxiliary role in monitoring patient compliance in treatment. While an early small-scale study showed a limited predicting value for sweat test in CF therapy with ivacaftor [8], a large-scale analysis later demonstrated a good correlation between sweat chloride concentration and ppFEV1 among patients treated with ivacaftor [9].

The use of a CFTR function-based airway biomarker such as NPD will provide additional insights concerning a specific

patient's status of lung pathophysiology. A major drawback of NPD is that this test is more difficult to perform and requires more specialized staff in order to get accurate measurements. Other airway biomarkers can provide additional information on irreversible airway damage, strains and severity of bacterial infection, airway inflammation, and mucociliary clearance [10]. Such biomarkers can be useful in the development of antibiotics and anti-inflammatory drugs for CF patients [11].

Intestinal *ex vivo* biomarkers provide a unique opportunity to directly assess the impact of different pharmacological agents on CFTR activity in a specific patient with defined genomic background [12]. They include ICM and a recently developed intestinal organoid assay. A similar approach is being used to obtain primary cultures of nasal or bronchial epithelial cells from specific CF patients. The procured cells can be biobanked for long-term studies including future therapeutic studies, eliminating the need for more samples from the same patient. Such an *ex vivo* approach provides precious clinical materials to assess drug responses of patients with a defined CFTR genotype. Given the highly diversified CFTR genotypes among CF patients and the limited number of patients with a specific genotype, this approach will prove essential in the development of drugs that treats rare CF mutations.

Genomics, transcriptomics, proteomics, metabolomics, lipidomics, glycomics, and microbiota are accelerating the identification of novel CF biomarkers [13], which can be included to provide precision and personalized treatment for individual CF patients. With the multiple, long-term and simultaneous medications CF patients are taking, and with the advent of increasingly efficacious combinational CFTR modulators, a large array of clinically relevant, tissue-specific CF biomarkers will be highly useful in sorting out the mechanisms of action, drug-genome interactions, and drug-drug interactions in CF therapy at the system level.

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REFERENCES

1. Riordan JR, Rommens JM, Kerem B, Alon N, Rozmahel R, Grzelczak Z, et al. Identification of the cystic fibrosis gene: Cloning and characterization of complementary DNA. Science. 1989; 245: 1066-1073.
2. Pettit RS. Cystic fibrosis transmembrane conductance regulator-modifying medications: The future of cystic fibrosis treatment. Ann Pharmacother. 2012; 46: 1065-1075.
3. Wainwright CE, Elborn JS, Ramsey BW, Marigowda G, Huang X, Cipolli M, et al. Lumacaftor-Ivacaftor in patients with cystic fibrosis homozygous for Phe508del CFTR. N Engl J Med. 2015; 373: 220-231.
4. Taylor-Cousar JL, Munck A, McKone EF, van der Ent CK, Moeller A, Simard C, et al. Tezacaftor-Ivacaftor in patients with cystic fibrosis homozygous for Phe508del. N Engl J Med. 2017; 377: 2013-2023.
5. De Boeck K, Kent L, Davies J, Derichs N, Amaral M, Rowe SM, et al. CFTR biomarkers: Time for promotion to surrogate end-point. Eur Respir J. 2013; 41: 203-216.
6. Guimbellot J, Sharma J, Rowe SM. Toward inclusive therapy with CFTR modulators: Progress and challenges. Pediatr Pulmonol. 2017; 52: S4-S14.
7. van Koningsbruggen-Rietschel S, Naehrlich L. Cystic fibrosis transmembrane conductance regulator biomarkers in 'real life': Can we evaluate individual efficacy of cystic fibrosis transmembrane conductance regulator therapy? Therapeutic advances in respiratory disease. 2015; 9: 198-200.
8. Barry PJ, Jones AM, Webb AK, Horsley AR. Sweat chloride is not a useful marker of clinical response to ivacaftor. Thorax. 2014; 69: 586-587.
9. Fidler MC, Beusmans J, Panorchan P, Van Goor F. Correlation of sweat chloride and percent predicted fev1 in cystic fibrosis patients treated with ivacaftor. J Cyst Fibros. 2017; 16: 41-44.
10. Muhlebach MS, Clancy JP, Heltshe SL, Ziady A, Kelley T, Accurso F, et al. Biomarkers for cystic fibrosis drug development. J Cyst Fibros. 2016; 15: 714-723.
11. Elborn JS, Horsley A, MacGregor G, Bilton D, Grosswald R, Ahuja S, et al. Phase I studies of acebilustat: Biomarker response and safety in patients with cystic fibrosis. Clin Transl Sci. 2017; 10: 28-34.
12. Beekman JM, Sermet-Gaudelus I, de Boeck K, Gonska T, Derichs N, Mall MA, et al. CFTR functional measurements in human models for diagnosis, prognosis and personalized therapy: Report on the pre-conference meeting to the 11th ECFS basic science conference, Malta, 26-29 march 2014. J Cyst Fibros. 2014; 13: 363-372.
13. Finch S, Keir HR, Dicker AJ, Chalmers JD. The past decade in bench research into pulmonary infectious diseases: What do clinicians need to know? Respirol. 2017; 22: 1062-1072.

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