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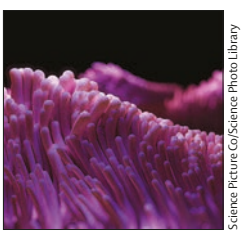
Primary ciliary dyskinesia treatment: time for a new approach?

Primary ciliary dyskinesia and cystic fibrosis share the feature of compromised mucociliary clearance, which results in defective airway defence.[1] Both conditions are characterised by a respiratory phenotype of recurrent-to-chronic infections with progressive lung function decline, although in most people with cystic fibrosis, the clinical course is worse than in primary ciliary dyskinesia.[1,2] Cystic fibrosis is a genetic disorder in which the main manifestations derive from altered function of the cystic fibrosis transmembrane conductance regulator (CFTR), a protein that modulates the extracellular movement of Cl^-.[3] By contrast, primary ciliary dyskinesia pathophysiology derives from mutations in several genes that encode proteins for motile cilia; highly complex molecular processes allow synchronous beating of motile cilia, which generates directional fluid flow, in healthy individuals.[4] Genetic mutations have been detected in about 65% of people with a diagnosis of primary ciliary dyskinesia.[5] So far, variants of approximately 50 primary ciliary dyskinesia genes have been discovered, and the research efforts suggest that, particularly in people with typical symptoms but healthy ciliary ultrastructure, other genes will be identified. Even though impaired mucociliary clearance related to primary ciliary dyskinesia derives from cilia dysfunction, and not from the reduced airway surface layer secondary to CFTR abnormalities that occurs in cystic fibrosis, the ultimate event leading to a similar respiratory phenotype in the two conditions is the production of dehydrated secretions.[1] Therefore, primary ciliary dyskinesia treatment has, historically, been based on interventions for cystic fibrosis, and a symptom-based strategy, including early aggressive treatment of exacerbations and chest physiotherapy, is the cornerstone of primary ciliary dyskinesia management.[4] Compared with the large number of cystic fibrosis clinical trials, few controlled trials for primary ciliary dyskinesia have been undertaken—some with excellent findings[6,7] and others with less convincing results.[8]

In the past two decades, supported in part by an enormous financial investment from the US Cystic Fibrosis Foundation, an exceptional research effort has led to an acceleration in the understanding of CFTR biology.[9] The development of so-called highly effective modulator therapies, which are able to target specific mutations and correct CFTR dysfunction, was the result of this extraordinary effort.[3] CFTR modulator therapy has transformed the cystic fibrosis therapeutic landscape, substantially improving life expectancy and quality of life in an increasing number of patients.[9] The increasing application of mutation-specific drugs has confirmed the importance of personalised treatment in cystic fibrosis,[3] and a similar approach in primary ciliary dyskinesia—targeting the effects of gene variants that underlie the development and progression of disease—might be within reach, which would reduce the need for extrapolation from cystic fibrosis. However, although the search for disease-specific therapeutic targets should be a priority in primary ciliary dyskinesia, the complex and still largely unknown genetic background of ciliary dysfunction and the absence of substantial investments in the field continue to limit the development of novel effective therapeutic strategies for primary ciliary dyskinesia.[10]

In *The Lancet Respiratory Medicine*, Felix Ringshausen and colleagues[11] report the results of the phase 2a CLEAN-PCD placebo-controlled crossover trial in adolescents and adults with primary ciliary dyskinesia, in which they tested the effects of idrevloride, a nebulised epithelial sodium channel (ENaC) blocker, with or without hypertonic saline. The authors' rationale for the study was based on the assumption that the reabsorption of Na^+ in the healthy airway epithelium is regulated by ENaC,[1] and on the finding from in-vitro studies on normal and primary ciliary dyskinesia bronchial cells that reduced ENaC activity enhances mucus hydration.[12] They hypothesised that the combination of inhaled idrevloride with hypertonic saline would improve mucociliary clearance by increasing the hydrating effect of hypertonic saline on mucus. The main finding of the CLEAN-PCD study was a small improvement in lung function after 28 days of treatment in patients receiving idrevloride plus hypertonic saline over those receiving one of the two components alone or placebo (part A). Probably because of the small increase in FEV_1, no change in participants' quality of life was detected. In the second part of the study (part B), the optional addition of the CFTR potentiator ivacaftor in a small subset of participants for 28 days resulted in increased FEV_1 only in participants given idrevloride plus hypertonic saline, but not in those receiving placebo.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Despite the limitations of the study—including high participant dropout throughout the study and the short-term assessment of the outcome measures—this trial represents a commendable attempt to move the target of primary ciliary dyskinesia therapeutic strategies from the effects of the disease to the underlying mechanisms. The ambitious idea of a drug-induced change in mucus rheology is not entirely new. However, unlike in cystic fibrosis, the results of a few studies testing drugs (eg, dornase alfa or N-acetylcysteine) targeting primary ciliary dyskinesia mucus properties have been disappointing.[10] Although novel, the attempt to increase the efficacy of inhaled idrevloride plus hypertonic saline by administering ivacaftor did not lead to notable benefits. This result is not surprising. Unlike in other conditions such as chronic obstructive pulmonary disease,[13] no secondary CFTR dysfunction has been shown in primary ciliary dyskinesia, and the rationale for repurposing of this CFTR potentiator in primary ciliary dyskinesia is questionable. In conclusion, at present, treatments that might represent for primary ciliary dyskinesia what CFTR modulator therapy is for cystic fibrosis are still difficult to imagine.

Understanding of primary ciliary dyskinesia genetics has improved substantially and, with an increasingly detailed definition of the role of specific gene mutations, potential genotype–phenotype relationships have emerged.[5] In-vitro data from gene therapy or gene editing showing the partial restoration of ciliary function are encouraging, but the clinical effects of these approaches have not been assessed so far.[10] Despite the promising findings of the CLEAN-PCD study, further evidence is needed before formal recommendations for treatment are made; however, these data offer the opportunity to rethink primary ciliary dyskinesia treatment and emphasise the relevance of testing new therapeutic approaches that might act at a deeper level, targeting the mechanisms of disease, than those currently applied.

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