Modifier Genes in Cystic Fibrosis: can they be found in the Intestinal Metagenome?

Michel Chignard*

Sorbonne Université, UPMC Univ Paris 06, Inserm, Centre de Recherche Saint-Antoine Paris, France

*Address for Correspondence: Michel Chignard, Sorbonne Université, UPMC Univ Paris 06, Inserm, Centre de Recherche Saint-Antoine Paris, France, E-mail: chignard@pasteur.fr

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CF is recognized as the disorder of a single gene, the Cystic fibrosis transmembrane conductance regulator. However, patients who have the same variants in CFTR exhibit substantial phenotypic variations. Thus, a considerable diversity in the clinical phenotype has been documented. Identification of additional gene alleles, so called «modifier genes» that directly influence the phenotype of CF disease became a challenge, not only for the insight it provides into the CF pathophysiology, but also for the development of new potential therapeutic targets [1].

One of the most studied phenotypes is the lung disease severity as lung dysfunction is the major cause of morbidity and mortality in CF patients. Thus, patients with the same CFTR variants may exhibit differences in the severity of their lung disease, of which >50% is explained by non-CFTR genetic variation [2]. A variety of measures have been devised to assess severity of lung disease. The forced expiratory volume in 1 sec (FEV₁) is the most clinically useful measure of lung disease severity and is a measure of small and large airway obstruction, the major site of disease in CF [3]. Furthermore, FEV₁ can track progression of obstruction and is well correlated with survival. This lung function measure is highly variable among CF patients with identical CFTR genotypes (e.g., F508del homozygotes) and is considered as a key index for the involvement of modifier genes.

The current challenge for many studied monogenic disorders is to assess the relative contribution of genetic factors distinct from the disease-causing gene and to identify those genes that modify outcome. Two main genetic approaches have mainly been explored so far [1]: an “a priori” approach, i.e. the candidate gene approach [2]; a “without a priori” approach, analysing the whole genome by linkage and genome-wide association studies (GWAS), or the whole exome by exome sequencing [4].

Using the latter approach, Corvol et al. [5] identified from 6,365 patients five modifier loci of lung disease severity in CF. Such discoveries of modifier loci that are strongly associated with severity of CF lung disease provide an opportunity to enhance individualized treatment in CF.

But could not the intestinal metagenome be the seat of some modifier genes?

The Intestinal Metagenome

With the use of metagenomic sequencing by the next-generation sequencing technology, progress has been made in the study of the human intestinal microbiome. This microbiome can now be characterized in unprecedented details by high-throughput sequencing of total stool DNA [6].

The importance of this new knowledge is that the compositional and functional changes of this microbial ecosystem are correlated with a variety of human pathologies [7]. Moreover, quantitative metagenomic analysis allows for the development of powerful algorithms to diagnose a disease, monitor patients and identify individuals at risk to progress towards a disease. Functional metagenomics can also identify novel functional genes, microbial pathways, antibiotic resistance genes, functional dysbiosis of the intestinal microbiome, and determine interactions and co-evolution between microbiota and host [8].

This lays ground for developing new approaches to better restore and even preserve the health by modulation of the altered microbiome, which contributes to promote or aggravate a disease.

Working Hypothesis: One or Several Intestinal Microorganisms are Modifiers of the Host Phenotype

Background

Recent data indicate that the intestinal microbiota has a remote effect on the immune activity in the lung. In fact, a demonstration
of a link between the gut microbiota and the respiratory outcome in CF patient has been published by Hoen et al. [9]. It is now believed that studying the interactions between intestinal microbiota and circulating immune cells can lead to the identification of therapeutic targets for chronic respiratory diseases [10].

Hypothesis

From the literature, it is established that the intestinal metagenome of CF patients is quite different from that of healthy people [11,12], which may have a remote effect on the lung immune capacity with as a consequence a higher susceptibility to infection and subsequently a lower respiratory ability.

To go further, one can speculate that according to the variability of the intestinal metagenomic composition in richness and abundance, the respiratory ability of the CF patients is different. In other words, such variations in microorganism composition would act as modifiers of the phenotype of CF patients.

Possible experimental design

In order to verify this hypothesis, one could analyse the intestinal metagenomes of patients with the very same CFTR variant and stratified them according to their FEV1.

Stools could be collected, processed and analysed from two groups of age-matched patients, one including mild CF patients with a high FEV1 (% predicted) with a mean value around 90 for the group, and another one including severe CF patients with a low FEV1 (% predicted) with a mean value around 40 for the group.

The hypothesis would be verified if there is a statistically significant different composition either in richness or abundance of microorganisms between the two groups. In such case, another kind of modifier genes would be involved i.e. modifiers of prokaryote origin.

Of note, variable other phenotypes could be looked at for a possible correlation with the intestinal metagenomics data, i.e., diabetes, liver dysfunction, BMI.

The Major Hurdle to Tackle

In chronic infections, pulmonary exacerbations require parenteral bi-antibiotic therapy (β-lactams or quinolones and aminoglycosides) for 15 to 21 days, inhaled antibiotics between the cures being useful to a consequence a higher susceptibility to infection and subsequently a lower respiratory ability.

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In chronic infections, pulmonary exacerbations require parenteral bi-antibiotic therapy (β-lactams or quinolones and aminoglycosides) for 15 to 21 days, inhaled antibiotics between the cures being useful to decrease the number of exacerbations. Thus, CF patients are regularly treated with antibiotics, and antibiotics compromise the microbiota [13]. Nonetheless, depending on the antibiotic molecule and its route of administration the microbiota may return to pre-treatment level between 2 weeks and 2 months [14]. These parameters have to be taken in consideration for the collection of the stools such as in the study of Hoen, et al. [9], in which detailed antibiotic exposure data were collected and used to adjust linear mixed effects models of changes in the microbiome development. Besides, antibiotics and new treatments (CFTR correctors an potentiators for instance), the design of such a study requires considering different factors such as age, sex gender, diet etc. All of these variables could of course influence the results and have to be considered in the analysis.

Therapeutic Perspectives: Fecal Transplantation and/or Specific Probiotics

Thus, another kind of modifier genes would play a role, modifiers from prokaryote origin and not from eukaryote origin.

A recent survey of the literature [15] indicates that ingestion of probiotics may improve respiratory and gastrointestinal outcomes in a stable CF clinic population with no reported evidence of harm. Nonetheless, there is inadequate evidence at this time to recommend a specific species, strain or dose of probiotic as likely to be of significant benefit.

It can be thus foreseen from the present proposed study that one or several microbial species (either bacteria, fungi or virus) could be identified of potentially playing a role in the remote control of an efficient immunity of the lung. As a consequence, the therapeutic treatment of patients by fecal transplantation containing appropriate beneficial microorganisms or administration of “good” specific probiotics could be contemplated.

References