Reply to: Individuality of the composition of the human microbiota

by Fernández-Estupiñán *et al*.

Sirs,

We thank Dr Fernández-Estupiñán *et al*. for their interest in our paper (1, 2) and for sharing their point of view on the complexity of human microbiota and how this should be considered in studies aimed at its characterisation.

We believe that a complete assessment of the microbiota in a specific state or disease should consider the reciprocity and the dynamism of the relationship between microorganisms inhabiting the human body and the host.

As pointed out by colleagues, there is evidence of a strong individual component of the composition of the gut microbiota. In this sense, we think that one of the main determinants could be the personal genetic background which, expressing itself through the metabolic and immune structure of each individual, could maintain and modulate the initial "core" microbiota present from birth. Recently, efforts have been made also in defining a "common denominator" through the detection of the basic human enterotypes (3) even of the human pan-microbiome (4), and in demonstrating their relative stability over time (5).

At the same time, part of the intestinal microenvironment is characterised by a significant variability, leading to a rapid and effective ability to adapt in response to external strains such as drugs and infections among the others (6). A convincing proof of this is represented by our ability to effectively modulate the microbiota through specific interventions such as diet, probiotics or faecal microbiota transplantation (7).

We are aware that this complexity could make the results of correlation studies - based on the analysis of relative abundance - difficult to interpret and generalise. The demonstration of an ongoing cause-and-effect relationship in the course of any disease cannot go beyond speculation in most of the cases. For this reason, proof-of-concept studies, although more complex in their implementation, are needed (8).

In our study, restrictive selection criteria were applied, in order to limit the amount of variability due to the abovementioned factors and by including the most representative population in line with our regional reality as regards demographic characteristics. Eventually we evaluated patients with altered body mass index. We have chosen this type of approach because systemic sclerosis is a rare disease and, especially in a single-centre study, the inclusion of an adequate number of patients for each different ethnic and cultural subset would have been unfeasible. However, the evaluation of data from cohorts of systemic sclerosis of different origin (American, Scandinavian, Mediterranean) reassuringly shows a certain consistency and the existence of a specific microbial signature, at least for observations concerning the analysis of relative abundances (9).

In our view, these data represent a promising starting point for future developments. We agree that these results should be validated on larger cohorts and ethnic groups other than those studied so far. The research agenda should also focus on further investigating functional correlates, both at gene expression and final metabolic products level, and on deciphering the possible role of specific pathogens within the entire microbiota, for example with studies in culturomics. Finally, longitudinal studies are strongly needed to broaden the knowledge and the possibility of intervention in this orphan disease.

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