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The microbiome as a human organ

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Abstract

The human organism is a complex structure composed of cells belonging to all three domains of life on Earth, Eukarya, Bacteria and Archaea, as well as their viruses. Bacterial cells of more than a thousand taxonomic units are condensed in a particular functional collective domain, the intestinal microbiome. The microbiome constitutes the last human organ under active research. Like other organs, and despite its intrinsic complexity, the microbiome is readily inherited, in a process probably involving 'small world' power law dynamics of construction in newborns. Like any other organ, the microbiome has physiology and pathology, and the individual (and collective?) health might be damaged when its collective population structure is altered. The diagnostic of microbiomic diseases involves metagenomic studies. The therapeutics of microbiome-induced pathology include microbiota transplantation, a technique increasingly available. Perhaps a new medical specialty, microbiomology, is being born.

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We are pleased to introduce the present collection of short reports which correspond to the presentations of the 18th Scientific Symposium of the Lilly Foundation Spain, entitled 'Microbiome: Deciphering the Last Organ of the Human Body'. This title emphasized an important concept: the microbiome can be regarded as a human organ from the physiological standpoint. Medicine has developed organ-based specialties such as nephrology, hepatology, cardiology or pneumology. Perhaps we can envisage 'microbiomology' as a future specialty of or a branch of clinical microbiology, devoted to the study of the physiology, pathology, diagnostics, therapy and prevention of alterations of the community structure of the microbiome.

The human organism, like most living organisms, is the result of stable associations among cells of different origins and genetic lineages, from mitochondria inside the cells in the tissues to the microbiota attached to the surfaces of the human body, integrating members of all three domains of life on earth, Eukarya, Bacteria and Archaea, and their viruses. We are definitely not a 'super-organism' (a term with inappropriate Nietzchean reminiscences), but just a complex organism with a diversity of genetic compositions. Indeed the microbiota composition and its relation with the gut have resulted from the dynamics of selection and competition [1].

Organisms are identified by their ability to replicate in well-defined specific lineages. The 'human lineage' (human cells, including mitochondria) is obviously transmitted by vertical descent, but the human microbiota is also transmitted to the progeny in a less specific but highly reproducible way, thus giving rise to a consistent heritage of a common core microbiome with inter-personal variations maintained over generations within a kinship [2].

As the microbiome is a highly complex structure, involving several thousands of different bacterial taxonomic units and therefore millions of links between them, the question emerging is how this complexity can be inherited.

Stanley Milgram (1933–1984), a social psychologist, was teaching a long time ago the concept of 'small world', illustrated by the 'six degrees of separation' thought experiment. Everyone is on average approximately only six steps away, by way of introduction, from any other person on Earth.

This happens because there are important nodes ('hubs') in the relational network that help to find other nodes, and the access to each new node creates new possibilities of finding individuals, to a certain extent along a power law dynamics. The application of this concept (without literally taking into account 'six steps') to the rapid building-up of the extreme complexity of human microbiota is illustrated in Fig. 1. In humans, a number of 'starting' bacteria such as *Lactobacillus*, *Prevotella* or *Sneathia* might be acquired during vaginal delivery [3,4] and possibly other pioneering populations are acquired by breast feeding [5]. It might be suggested that these early colonizers serve as sinks or attractors for other microbial partners (open curves in Fig. 1), and those for others thereafter; eventually pairs or higher consortia of organisms create novel niches for other organisms. The corresponding law of attraction remains one of the most important items to be investigated in microbiome biology [5], but it might relate to genomic functional complementarity following genetic reductions, following a model proposed for bacteria–eukaryotic cell coevolution [6]. As in the 'small world' metaphor, a complex system can be constructed rapidly and specifically. Note that, as in an integrated puzzle, the same system can be constructed from different nodal origins.

As in other fields of medicine, pathology frequently reveals the physiology of a system by illustrating the consequences of alterations and deficiencies. The importance of the microbiome has been highlighted by the microbial 'abnormalities' found in pathological conditions such as inflammatory bowel diseases, obesity or malnutrition.

Diagnosis of microbiome diseases is based at present on full metagenomic DNA sequencing and computational advances that can inform about and differentiate core microbiota and changing microbiota [7,8]. These 'diagnostic' techniques should also be able to evaluate the role of mobile genetic elements, which deeply influence the connectivity of the microbiome [9,10].

The therapy of microbiome diseases will be part of future interventions based on eco-evo drugs and strategies [11]. The use of prebiotics and probiotics to 'equilibrate' altered human microbiota represent rather empirical approaches which require much more basic and clinical research to advance on a scientific basis [12]. Addressing microbiome restoration by transplantation is crucial to advance in the curing of microbiome diseases. This approach has already been used, with very limited adverse effects, [13] for treating microbiome diseases such as *Clostridium difficile* associated pathologies, inflammatory bowel diseases, metabolic syndrome, obesity,

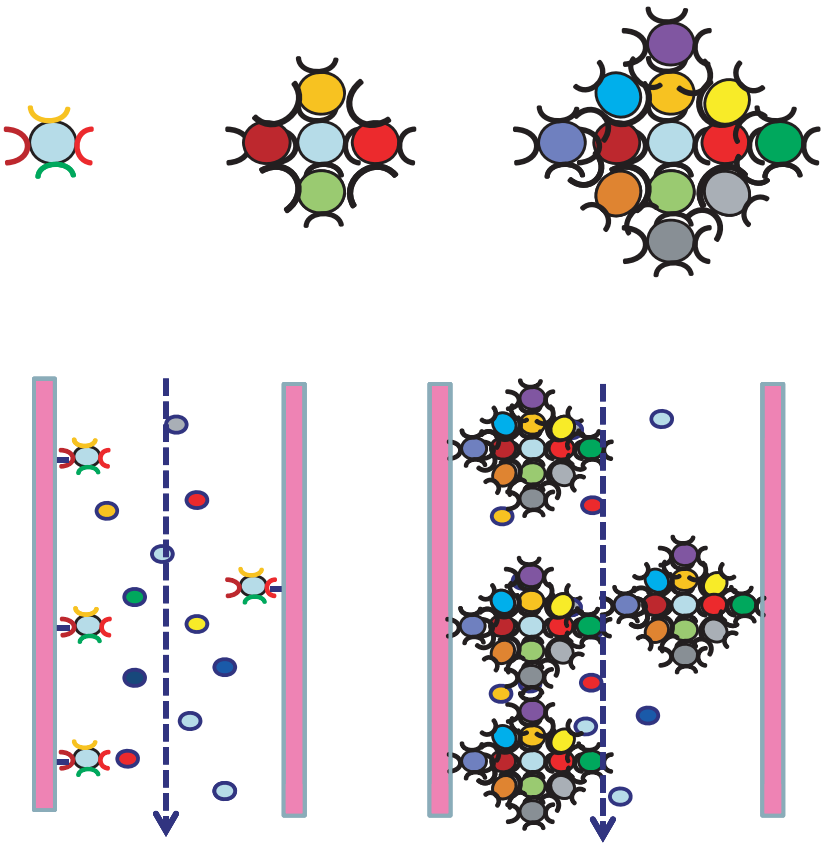

FIG. 1. 'Small world' hypothetical steps for the construction (reproduction) of microbiota. Upper part, left, a bacterial organism exposing 'attractors' (open curves) for other bacterial partners in the consortium; in the middle, the partners are present and themselves expose a variety of novel attractors, and the process progresses with a power law dynamics on the right. Lower part, the same schema applied to intestinal colonization; the host-attached pioneer population or community serves as attractor for other bacterial organisms circulating in the open system that are progressively inserted in the complex system.

neurodegenerative diseases and autoimmune and allergic diseases [4,14,15]. The possibility of engrafting new microbiota from a donor source [16] has been demonstrated. Fourteen days post-transplantation, the recipient microbiota was shown to be highly similar to the donor [17]. Progress in this field will be facilitated by using frozen preparations ready for transplantation [18] and experimental animal models [19]. Microbiota transplantation might also alter host resistance to infections [20].

A more advanced field of research in the therapy of microbiome diseases will be the discovery of drugs acting on host–microbiome and intra-microbiome signals and interactions [21]. However, we reiterate that little is known about the biochemical signals and micro-ecological structures assembling the different bacterial populations, and the bases for their maintenance and coordinate functionality [5].

The fascinating field of microbiome research has just started to yield knowledge of the multiple consequences of the alteration of the full microbial complement, a real organ, which is part of the human body. The relevance for human body and even human behavioural health will continue to be revealed in the years to come [2]. This research will stimulate integrative thinking to understand integrative complex structures and will importantly contribute to provide insights in a future 'grammar of life' research. Welcome to microbiomology!

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Transparency declaration

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References

1. Angelakis E, Armougom F, Million M, Raoult D. The relationship between gut microbiota and weight gain in humans. *Future Microbiol* 2012; 7: 91–109.
2. Gonzalez A, Stombaugh J, Lozupone C et al. The mind–body–microbial continuum. *Dialogues Clin Neurosci* 2011; 13: 55–62.
3. Dominguez-Bello MG, Costello EK, Contreras M et al. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. *Proc Natl Acad Sci U S A* 2010; 107: 11971–11975.
4. Reid G, Younes JA, Van der Mei C et al. Microbiota restoration: natural and supplemented recovery of human microbial communities. *Nature Rev Microbiol* 2010; 9: 27–38.
5. Robinson CJ, Bohannan BJM, Young VB. From structure to function: the ecology of host-associated microbial communities. *Microb Mol Biol Rev* 2010; 74: 453–476.
6. Moya A, Gil R, Latorre A. The evolutionary history of symbiotic associations among bacteria and their animal hosts: a model. *Clin Microb Infect* 2009; 15 (suppl 1): 11–13.
7. Caporaso JG, Lauber CL, Costello EK et al. Moving pictures of the human microbiome. *Genome Biol* 2011; 12: R50.
8. Bogaert D, Keijser B, Huse S et al. Variability and diversity of nasopharyngeal microbiota in children: a metagenomic analysis. *PLoS ONE* 2011; 6: e17035.
9. Smillie CS, Smith MB, Friedman J et al. Ecology drives a global network of gene exchange connecting the microbiome. *Nature* 2011; 480: 241–244.
10. Jones BV, Sun F, Marchesi JR. Comparative metagenomic analysis of plasmid encoded functions in the human gut microbiome. *BMC Genomics* 2010; 11: 46.
11. Baquero F, Coque TM, de la Cruz F. Ecology and evolution as targets: the need of novel eco-evo drugs to fight against antibiotic resistance. *Antimicrob Agents Chemother* 2011; 55: 3649–3660.
12. Quigley EM. Prebiotics and probiotics: modifying and mining the microbiota. *Pharmacol Res* 2010; 61: 213–218.
13. Gough E, Shaikh H, Manges AR. Systematic review of intestinal microbiota transplantation (fecal bacteriotherapy) for recurrent *Clostridium difficile* infection. *Clin Infect Dis* 2011; 53: 994–1002.
14. Borody TJ, Khoruts A. Faecal microbiota transplantation and emerging applications. *Nat Rev Gastroent Hepatol* 2012; 9: 88–96.
15. Brandt LJ, Aroniadis OC, Mellow M et al. Long-term follow-up of colonoscopic fecal microbiota transplant for recurrent *Clostridium difficile* infection. *Am J Gastroenterol* 2012; 25: 45–89.
16. Khoruts A, Sadowski MJ. Therapeutic transplantation of the distal gut microbiota. *Mucosal Immun* 2011; 4: 4–7.
17. Khoruts A, Dicksved J, Jansson JK, Sadowsky MJ. Changes in the composition of the human fecal microbiome after bacteriotherapy for recurrent *Clostridium difficile*-associated diarrhea. *J Clin Gastroenterol* 2010; 44: 354–360.
18. Hamilton MJ, Weingarden AR, Sadowsky MJ, Khoruts A. Standardized frozen preparation for transplantation of fecal microbiota for recurrent *Clostridium difficile* infection. *Am J Gastroenterol* 2012; 107: 761–767.
19. Pang X, Hua X, Yang Q et al. Inter-species transplantation of gut microbiota from human to pigs. *ISME J* 2007; 1: 156–162.
20. Willing BP, Vacharaksa A, Croxen M, Thanachayanont T, Finlay BB. Altering host resistance to infections through microbial transplantation. *PLoS One* 2011; 6: e26988.
21. Shanahan F. Gut microbes: from bugs to drugs. *Am J Gastroenterol* 2010; 105: 275–279.