Gut microbiota — at the intersection of everything?

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Over the past decade, numerous studies have found an association between the gut microbiota composition and many diseases. However, is it reality? Or is the truth hidden in the shadow of several thousand publications a year with inflated expectations in almost any disease?

Nowadays, it is accepted that we are living with at least the same number of microorganisms as our own human cells[1]. According to the current literature, it is tempting to say that the gut microbiota are probably at the intersection of everything and all physiological or pathological situations. With >3,000 papers published alone in 2016 (PubMed search with the term "gut microbiota") compared with <90 in 2006, there is no doubt that the field has progressed. The gut microbiota composition, and to a lesser extent their metabolic activity, have been connected with many diseases, including disorders associated with obesity, chronic inflammatory diseases, cardiovascular disease, cancers, stress, and even neurodegenerative disorders (FIG. 1). Although the growing interest has exploded over the past 10 years, it is disappointing that published studies have mostly linked the gut microbiota with diseases as opposed to proving causation. Even more problematic, the overall assumption that the gut microbiota are causally linked with the onset or progression of a disease is often made following a unique measurement of the composition of the faecal microbiota (and sometimes metabolites) at a specific time point. Thus, the general conclusions assume that finding a different gut microbiota composition infers a strong association with a specific disease or the microbiota's overall evolution is often captured through only one snapshot. Few studies have investigated the variation of microbiota composition (and metabolites) and interactions with circadian rhythm, host genome, nutrition and dietary habits[2]. Comparing health and disease situations without clearly demonstrating causality, or at least strong evidence of any link, is a major issue. However, a few exceptions are available as studies have investigated the role of microbial metabolic activities, such as the production of short-chain fatty acids (acetate, propionate, butyrate), trimethylamine oxide[3], neurotransmitters or specific microbial membrane components (Toll-like receptor agonists or any active compounds)[4].

Are we exploring a novel organ?

Probably not! We could say that the microbiota represent a multiple set of 'organs' instead of only one organ, or a complex gearing system within another even more complex 'machine' that is the human (FIG. 1). Indeed, the key difference between the host organs and the microbiota 'organ' is that we still do not really know with precision the composition of this organ in terms of cells or even their role. Although we do not fully understand human physiology, our own organs are better characterized than the microbiota; for instance, host cells constituting an organ are organized in tissues with defined function(s). Unfortunately, when considering the gut microbiota, we are far from this picture. Indeed, much of the research does not take into account the exact role of this ecosystem and its dynamic evolution. The microbiota are permanently under the influence of many parameters, such as host birth and delivery conditions (Caesarean versus vaginal delivery), genetics, metabolism, immunity (innate and adaptive) and nutrition (FIG. 1). Notably, the latter is probably one of the most important and controllable factors that can shape the gut microbiota and their activity, and also influence how microorganisms will behave. In other words, we are still at the beginning of the story.

In obesity and metabolic disorders it was initially thought that a shift of the major phyla that are present in the vertebrate gut[5], that is Firmicutes and Bacteroidetes, was a simple and key marker of dysbiosis (that is, a deviation of the gut microbiota according to a 'normal' situation). But what is normal? What is a healthy gut microbiota composition and does it really exist? Although considered as too simplistic and probably not responsible for the phenotype observed (in terms of entire causality), observations on dysbiosis and obesity are no less significant than similar other methods of stratification of the human gut microbiota composition — that is the enterotypes, gene richness or even gene count — that also do not fully depict the reality of the situation[6].

Altogether, these data strengthen the view that we are lacking the full understanding of the constellations of gut microorganisms that are in our gut. Novel microbial strains could be isolated from the human gut, some are part of a core microbiota, some are simply newly identified. It is, therefore, tempting to simply compare the

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doi:10.1038/nrgastro.2017.54
Published online 26 Apr 2017

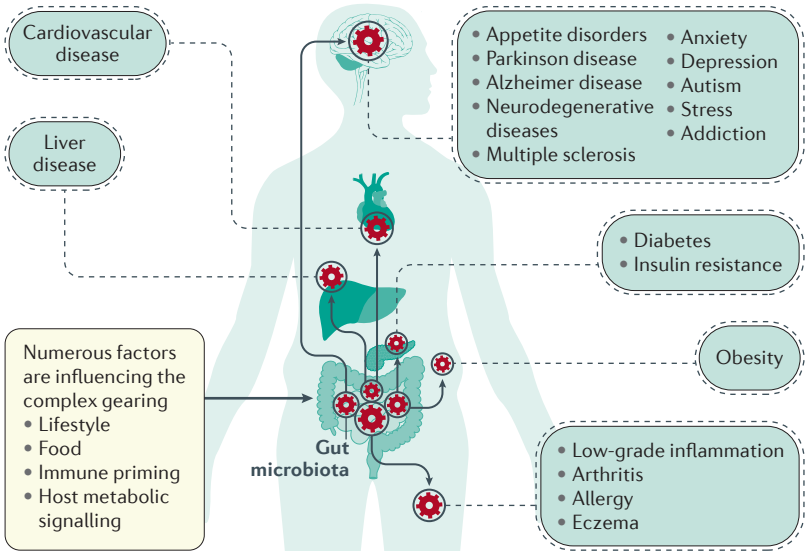

Figure 1 | **Gut microorganisms at the intersection of several diseases.** Gut microbiota composition and activity are under the influence of numerous factors (e.g. lifestyle and host metabolic activities). In numerous studies, the gut microbiota were found to be affected in a vast number of pathological situations. Whether the complex gearing of the gut microbiota and other cell types and organs are influencing each other is still debated. Deciphering the number and respective effect of each 'cog' on the overall human metabolism might lead to novel therapeutics, and overall host physiology could be considered a gearing with every cell type potentially able to influence another.

discovery of a novel microbial partner with the discovery of novel cell type in a host organ, as with a novel cog in a gearing. Deciphering the role of this cell (or bacterium) will require extensive work, and it is probably premature to say that today we understand exactly how the gut microbiota are working, especially in disease.

Coming back to host physiology, several decades of investigations have been required to determine the key levels of blood glucose that should be achieved to limit the effects on cardiovascular risk, neuropathy and kidney diseases[7,8]. Still, although we know with a certain precision the level of glycaemia that we should reach to prevent or to delay such diseases, glucose is not a unique player in the disease process, with many other partners involved (such as lipids, cellular metabolism and immune cells). Do we know the best gut microbial composition expected to prevent specific diseases such as obesity or cancer? No, and this aspect will probably not be completely understood within the next decade.

More time for research to progress?

We should allow more time for microbiota research to progress, but we should also focus these research efforts. An important issue in the microbiota field is the over-expectation of results to be quickly translated into humans and with strong effect. But why should we expect more results from microbiome research than from any other research field? It is evident that we have progressed in analysis of the microbiota composition, discovering and isolating novel bacteria, but numerous papers report gut microbiota composition in different situations (healthy versus disease states or mode of delivery), which has led to misinterpretation or over-selling of the expected results when translated into humans. According to experts, this over-selling is highly detrimental for the field[9]. Instead of pushing the field at its vindicated level, dangerously surfing on the wave of the microbiome research without enough critical assessment could discredit the overall work done so far. One should expect better scrutiny from scientists, but also from editors and peer-reviewing processes to avoid such misunderstanding. The experience of this area of research thus far teaches us that it is not solely because one or several bacteria are increased or decreased in a specific pathological situation that suggests they have a role. Further research and careful investigation is needed to prove that replacing the missing microorganisms does indeed at least mitigate the disease, which should finally help to acknowledge that some specific observations might simply be collateral damage or a pure coincidence.

Are the microbiota at the intersection of everything? I am tempted to say yes, as it is plausible. As glucose and insulin have multiple roles in metabolism and physiology, we know now that both factors are intertwined and finely regulated: glucose levels are under the control of insulin levels and action, and are further influenced by endogenous glucose production, glucose entry and utilization in cells, several sensors, many hormones, lipid levels, and cell energy status. Still, we do not fully understand everything and the same considerations can be applied to the gut microbiota, their activity and role in disease.

Today we might be lacking strong evidence between gut microorganisms and some diseases, but that does not mean we will not be able to find evidence. If we expect to mitigate or even to cure some specific diseases by focusing our attention on the gut microbiota composition and/or their activity, we need to better understand the complex gearing processes in place first. Finally, more care should be taken when concluding that microbial changes directly affect host metabolism or disease progression to ensure that the conclusions are supported by the evidence.

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Acknowledgements
P.D.C. is a research associate at FRS-FNRS (Fonds de la Recherche Scientifique) and the recipient of grants from FNRS (convention J.0084.15, convention 3.4579.11), PDR (Projet de Recherche, convention: T.0138.14) and Walloon region DG06-FSO project (Microbes 1510053). His work is supported by the FRFS-WELBIO under grant: WELBIO-CR-2012S-02R, and, in part, by the Funds Baillet Latour (Grant for Medical Research 2015). P.D.C. is a recipient of POC ERC grant 2016 (European Research Council, Microbes4U_713547) and ERC Starting Grant 2013 (Starting grant 336452-ENIGMO).

Competing interests statement
The author declares no competing interests.