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Human intestinal metagenomics: state of the art and future

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Over the last few years our understanding of human biology has undergone profound transformation. The key role of the 'world inside us', namely the gut microbiota, once considered a forgotten organ, has been revealed, with strong impact on our health and well-being. The present review highlights the most important recent findings on the role of gut microbiota and its impact on the host and raises crucial questions to be considered in future studies.

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Introduction: an ongoing revolution with conceptual revisions

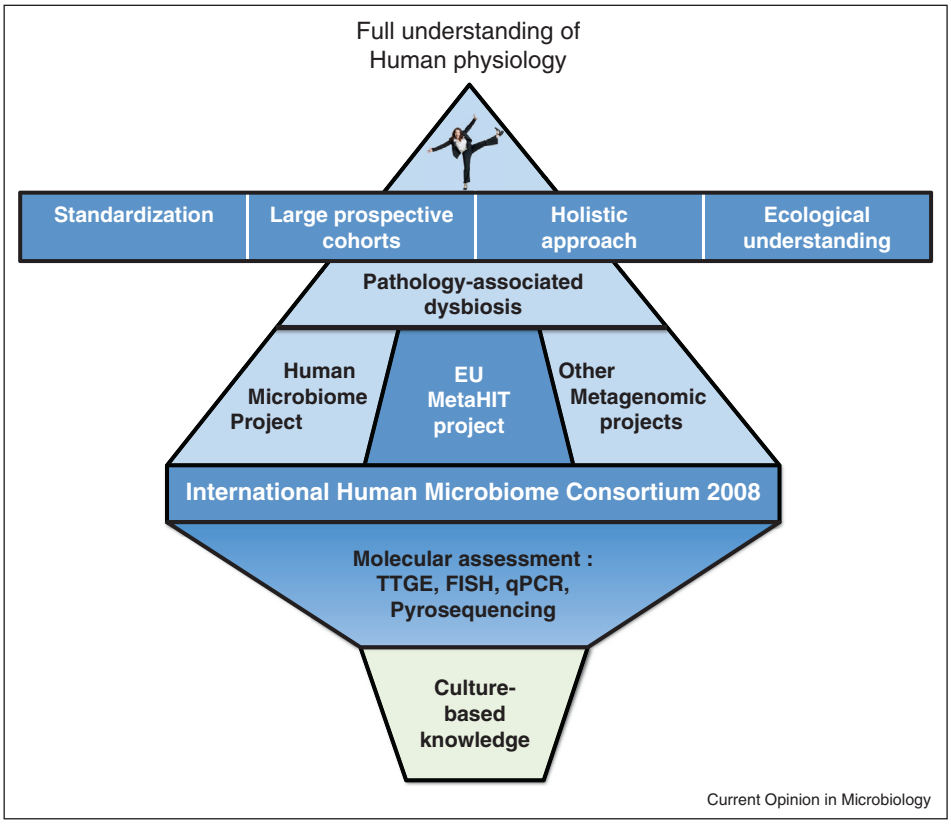
The human intestinal microbiota has recently gained its recognition as a true organ. Major reasons for this are its dense and diverse microbial population, its immense metabolic potential, its ability to interact with other tissues including immune and neural cells, and even more so, its amenability to transplantation. Assessment and characterization of its individual components has been restricted for a long time to anaerobic culture techniques. However, the development of molecular ecology, with emphasis on 16S rDNA-based approaches, has dramatically revised our vision of gut microbiota. By the end of the 1990s, PCR-based single gene libraries highlighted the huge proportion of yet uncultured species in the dominant human gut microbiota, stressing the existence of a unique arrangement for each human individual [1]. Ecological parameters were also substantiated such as the remarkable resistance to modification over time after early life developmental changes and possible alterations in the very old age. Responses to moderate stress such as antibiotic treatment even showed resilience of the microbiota illustrating its intimate association with the host [2]. By the turn of the century, whole shotgun sequencing of environmental DNA became available and was fairly rapidly applied to the human digestive system [3]. Major observations, partly unexpected, were made from the recent metagenomic exploration of the human intestinal microbiome that will be reviewed herein (Figure 1).

As the microbiota of healthy individuals was better understood, molecular ecology tools were applied to the comparative assessment of the gut ecosystem of patients and healthy controls. This was especially fruitful in the context of immune-mediated diseases that have shown a rise in incidence since the 1950s, which could not be explained by a drift in human genetics alone [4]. For many of these chronic diseases such as inflammatory bowel diseases, metabolic disorders, allergies, degenerative diseases and even neurological disorders, no single responsible factor has been identified as possible cause; however, a distortion in the composition of the commensal microbiota has been observed as a common trait for these conditions [5]. Beyond the now well supported existence of structural alterations of the microbiota in these patients compared to healthy individuals, here, we present recent findings linking disease with a loss of overall gene diversity, reminiscent of an organ's atrophy, and even an impaired or loss of molecular crosstalk between commensal bacteria and human tissues.

Microbiota development and impact of early events: the little we know

The first level of impact of gut microbiota on human health has been shown to occur during pregnancy. Indeed, Koren and colleagues revealed major modification of the mother's microbiota during gestation especially during the third trimester with increase in Proteobacteria and Actinobacteria and an overall reduced species richness [6•]. Moreover, it was demonstrated that this shift impacts directly on metabolic functions with increased energy storage in fat tissue, which should be beneficial for the mother as well as the fetus. What triggers these changes in gut microbiota during the third trimester remains elusive; however, it is tempting to associate it to major modification in mucosal immune functions during pregnancy.

Figure 1



Over the past decades, our knowledge on Human intestinal microbiota has been considerably transformed thanks to the technological progress. The creation of the International Human Microbiome Consortium in 2008 was an important step in sharing data and view. However, several challenges have to be addressed to fully decipher human physiology.

The establishment of a stable ecosystem is shaped during the first year of life [7,8]. The mode of delivery, that is, vaginal birth or C-section, the method of early feeding (breast or formula-feeding) and weaning are key factors that impact the diversity and richness of the microbiota with profound impact on health [9]. Early-life modification of the shaping of the ecosystem such as antibiotic exposure affects the long-term development of adipose tissue, lean muscle and bone [10•]. Studying healthy children and adults from Amazonas, Malawi and three metropolitan areas in the USA, Yatsunenko and colleagues reported common features during the first three years of life [11•]. However, major differences were noted for USA residents with a dramatic reduced biodiversity observed after three years of age and throughout life. This suggests an impact of lifestyle with potential cumulative effect over several generations. Settlement of the gut microbiota shapes not only the mucosal immune system [12,13,14•], but also the overall metabolic status [15,16]. Upon conventionalization, that is transfer of a mouse microbiota to germ-free mice, a major induction of the innate immune function in the ileum and colon was observed within four days. It was then followed by the stimulation of the adaptive immune response and, at a later stage, by the expansion of the adaptive T and B cells [14•]. Conventionalization was also associated with a dynamic control of the metabolic reorientation in the jejunum [15]. Moreover, this colonization process stimulated glycogenesis in the liver followed by hepatic triglyceride synthesis and associated modification of key genes such as Cyp8b1, Cyp3a11 or Cyp2c29 [16].

However, another key finding by Chung *et al.* indicated that the nature of the colonizing microbiota affects the host's initial T cell populations [17•]. By transferring human or mouse microbiota to germ-free mice, this work provides evidence of host-linked co-evolution of the microbiota and immune responses.

Normal microbiota (challenging definition)

The human intestinal microbiota harbors microorganisms belonging to all three domains of life. Key features supporting its recognition as a true organ of the host comprise: firstly, its intrinsic complexity; secondly, its