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The human gut microbiome, a taxonomic conundrum

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ABSTRACT

From culture to metagenomics, within only 130 years, our knowledge of the human microbiome has considerably improved. With >1000 microbial species identified to date, the gastro-intestinal microbiota is the most complex of human biotas. It is composed of a majority of *Bacteroidetes* and *Firmicutes* and, although exhibiting great inter-individual variations according to age, geographic origin, disease or antibiotic uptake, it is stable over time. Metagenomic studies have suggested associations between specific gut microbiota compositions and a variety of diseases, including irritable bowel syndrome, Crohn's disease, colon cancer, type 2 diabetes and obesity. However, these data remain method-dependent, as no consensus strategy has been defined to decipher the complexity of the gut microbiota. High-throughput culture-independent techniques have highlighted the limitations of culture by showing the importance of uncultured species, whereas modern culture methods have demonstrated that metagenomics underestimates the microbial diversity by ignoring minor populations. In this review, we highlight the progress and challenges that pave the way to a complete understanding of the human gastrointestinal microbiota and its influence on human health.

Introduction

The human microbiome is a complex and dynamic mixture of microorganisms that exceeds the total number of human cells by a factor 10, and by a factor 150 when considering the number or bacterial genes versus the human genome [49,71,110]. It is made of different microbial communities present in different parts of the human body such as the oro-naso-pharyngeal sphere, skin, vagina and gastrointestinal tract (GI) (Fig. 1), each of which interacts with its host and has an impact on human health and disease. The human GI microbiota is mostly concentrated in the colon and is made of a majority of bacteria, completed by few archae, eukaryotes and viruses [113]. However, it has been estimated that only 30% of the human GI microbiota was characterized [60], despite the growing interest of the scientific community for this topic, as evidenced by the increasing number of dedicated articles in the scientific literature.

Initial culture methods to decipher the complexity of the human microbiome have progressively been replaced by molecular methods, notably metagenomic studies of the human GI that revealed, at least partially, that the microbial diversity associated with humans was far from fully known (Fig. 2) [17]. However, these studies have also emphasized that the distribution of specific microbial communities and catalogs of genes among individuals could be influenced by several factors, including the geographical origin, age and diet of studied individuals as well as antibiotic or probiotic uptake [31,39,45,100,104,110,140,146,149]. In addition, associations between specific gut phyla and intestinal disorders, obesity or diabetes were also studied [62]. Recently, a renewed interest in culture methods for the study of the human microbiome was motivated by the drawbacks of molecular studies of the human microbiome, notably that minor populations (present in concentrations $<10^6$ mL^{-1}) were ignored [11] and that the characterization of the detected microorganisms was not reliable at the lowest taxonomic levels. Based on diversified culture conditions and coupled to mass spectrometry, methods such as the "culturomics" strategy demonstrated to be complementary to molecular tools and enabled the recovery of many previously unknown species and genera.

This review focuses on the successive methods used to characterize gut bacterial communities. The influence and limitations of these methods for the taxonomic classification of members of the gut microbiota are discussed.

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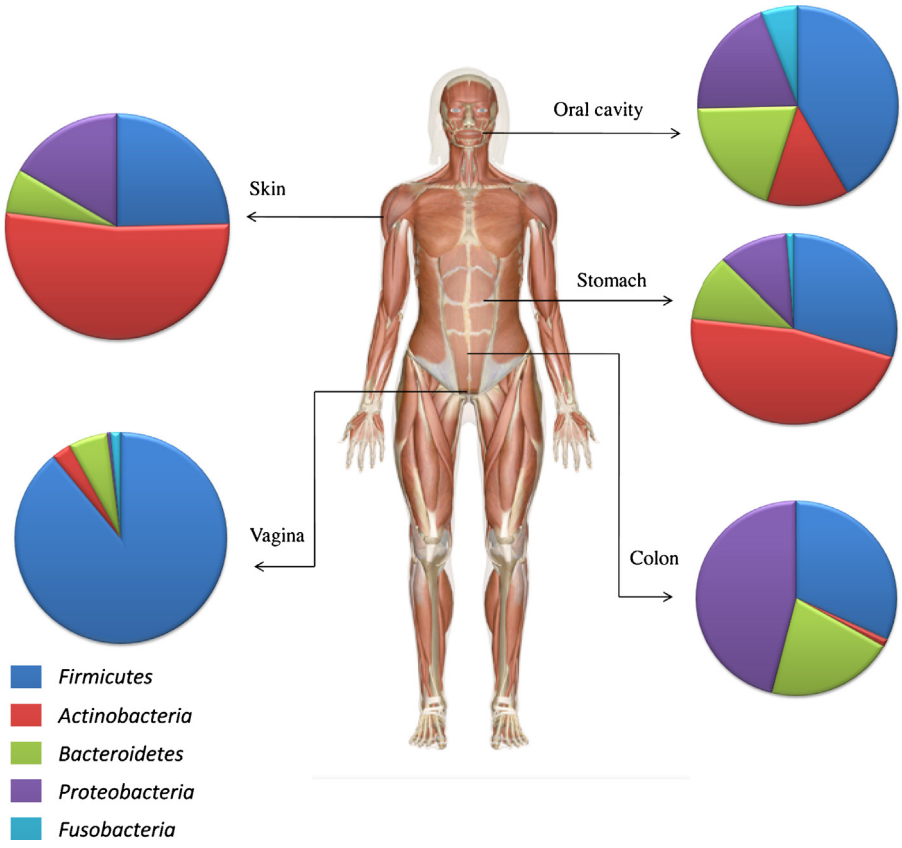

Fig. 1. Distribution of bacterial phyla in human body habitats (adapted from [4,6,27,44,119]).

The human gut microbiota

Among the trillions of human-associated microorganisms, bacteria are predominant and are distributed throughout the gastrointestinal tract (GI) [22]. Bacterial communities exhibit quantitative and qualitative variations along the length of the GI due to host factors (pH, transit time, bile acids, digestive enzymes, mucus, immune system), non-host factors (nutrients, medication and environmental factors) and bacterial factors (adhesion capacity, enzymes, metabolic capacity, as well as microbial co-evolution, interactions and competition) [21]. From stomach to colon, the bacterial biomass ranges from 10^{2-3} to 10^{11}–10^{12} cells/ml [152], approximately 95% being anaerobic bacteria and at least 1000 different species being listed to date [60,110,113]. Of the >30 bacterial phyla constituting the gut microbiota [115], seven account for the vast majority of detected species, including the *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, *Cyanobacteria*, *Fusobacteria*, *Proteobacteria*, and *Verrucomicrobia*, with the members of the former two being the most abundant [108]. In addition, the high concentration of microorganisms within the human gut plays a role in prokaryotic evolution and diversification, facilitating lateral gene transfer (LGT), chromosomal rearrangements, gene duplications and adaptation to the changing environment [48,76,136].

Several evolutionary and ecological processes shape the association between the host and microorganisms [71]. The gut colonization by microorganisms is influenced, early in childhood, by the mode of birth (vaginal or cesarean delivery) and the diet (breast feeding or not), and stabilizes by the age of 3 [102,150]. Later, the fecal biota may also be influenced by various factors, the most common being the geographical environment (although globalization of food products tends to reduce the impact of this factor, as suggested by the reduced GI microbiota diversity observed in populations from Europe and USA when compared to rural Africa and South America [24,118,162]), diet, age [163] and prebiotic, probiotic or antibiotic uptake [39,45,100,140,149], although some microbial species, in particular, those acquired early in life, remain stable, as demonstrated during a 5-year study [33]. In addition, the GI microbial composition has been proved to have a direct impact

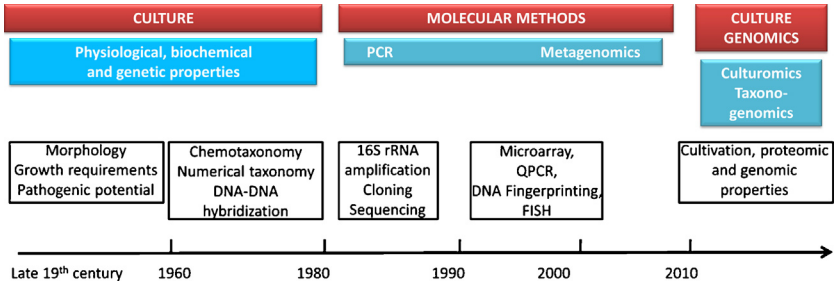

Fig. 2. Evolution of methods used to study the taxonomic diversity of human gut bacterial species. Red: microbiology era; Blue: main strategies and tools used to estimate the gut microbiota diversity; white: studied characteristics.