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Current Opinion in Genetics & Development

Insights into human evolution from ancient and contemporary microbiome studies

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Over the past decade, human microbiome research has energized the study of human evolution through a complete shift in our understanding of what it means to be human. The microbiome plays a pivotal role in human biology, performing key functions in digestion, mood and behavior, development and immunity, and a range of acute and chronic diseases. It is therefore critical to understand its evolution and changing ecology through time. Here we review recent findings on the microbiota of diverse human populations, non-human primates, and past human populations and discuss the implications of this research in formulating a deeper evolutionary understanding of the human holobiont.

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Current Opinion in Genetics & Development 2016, **41**:14–26

This review comes from a themed issue on **Genetics of human origin**

Edited by **Joshua Akey** and **Anna Di Rienzo**

http://dx.doi.org/10.1016/j.gde.2016.07.003

Introduction

Over the past decade, it has become increasingly clear that the study of human evolution is not complete without consideration of the human microbiome [1–3]. In addition to our own somatic cells, our bodies are a patchwork landscape that is home to thousands of different microbial species that number in the tens of trillions of cells [4•]. Rather than mere transient germs, these co-resident microbes contain an immense diversity of genes that interact directly with our physiology to carry out vital functions [5,6]. A growing awareness of these roles has resulted in a radical shift from thinking of human-associated microbes solely in terms of pathogenicity to considering them essential members of human biology [7,8] and a key component of the human holobiont [9].

Until very recently, human evolutionary genetics focused almost exclusively on patterns of variation found within our mitochondrial and nuclear genomes. Yet, the microbiome plays important roles in multiple core aspects of human biology, including digestion and energy metabolism, immune development, neurological function, and infectious disease susceptibility. As such, human-associated microbial communities (microbiota) and their microbial ecosystems (microbiomes) [10•] serve as accessory genetic reservoirs that are highly responsive to changes in human environments and lifestyles (Figure 1) and function as a shared target for natural selection. The growing body of knowledge on the relationship between the host genome, the microbiome, and the environment thus helps to answer fundamental questions about the role of microbial evolution and ecology in broader patterns of human evolution.

In this review, we discuss how recent human microbiome research informs work in human evolutionary genetics and how our understanding of human origins stands to benefit from a unification of both fields.

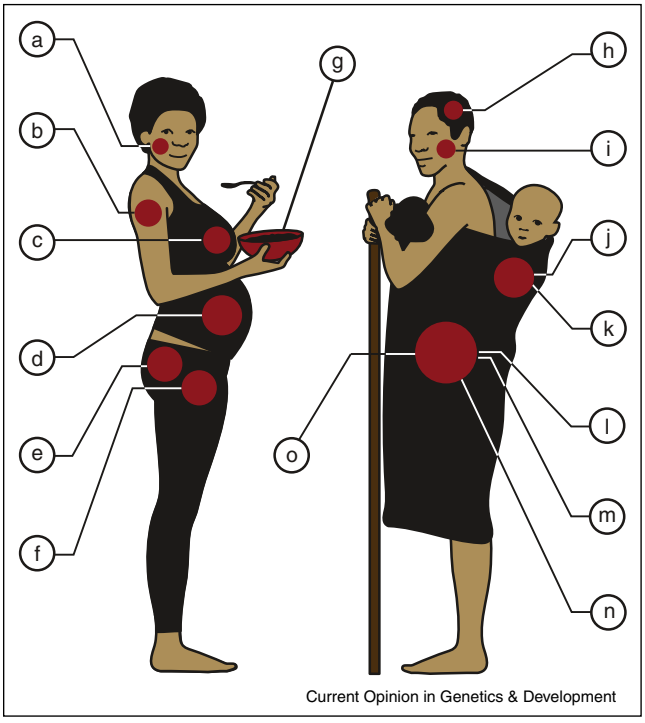
We also highlight how paleogenomics, the study of ancient genomes, is advancing our knowledge of the ancestral human microbiome and propose critical next steps forward.

Human microbiome research in context

With the conclusion of the Human Genome Project in 2003 [11] and successive efforts in whole genome sequencing of modern humans [e.g. [12]], archaic humans (including Neanderthals, Denisovans and the recently discovered Sima de los Huesos hominins) [13,14], and the great apes [15–18], comparative functional genomics has emerged as a leading research front poised to gain crucial insights into human-specific biology [19,20]. Complementing this endeavor, the Human Microbiome Project, initiated in 2007, leveraged advances in high-throughput DNA sequencing technologies to extend this research to the human microbiome [21].

Historically, the human microbiome has been generally overlooked in human genetics research, in large part due to the difficulty and complexity of characterizing microbial ecosystems using conventional molecular tools and

Figure 1



Overview of major functions of the human microbiome with evolutionary significance. **(a)** The oral microbiome a reservoir for numerous pathobionts and opportunistic pathogens [104,105,154]. **(b)** Skin microbiota influence mosquito attraction and may impact transmission of insect-borne diseases, such as malaria [138,139]. **(c)** Bacterial inoculation of the breast assists infants with milk digestion [31]; breastmilk contains human-specific oligosaccharides that promote the growth of beneficial gut bacteria [45–47,48••,49]. **(d)** The placenta harbors an oral-like microbiome [32]; oral and vaginal dysbioses increase risk for preterm labor and stillbirth [33,34]. **(e)** Human microbiota are hotspots for horizontal gene transfer [128•,129–131]; antibiotic resistance genes in oral and gut microbiota predate the use of therapeutic antibiotics [56•,104,127]. **(f)** Ecological structure of the vaginal microbiome influences risk for contracting sexually transmitted infections [137••]. **(g)** External microbial fermentation expands the food resources available to humans [94,99,100]; gut microbes play key roles in milk lactose [89] and wheat gluten [87,88,92] digestion and intolerance. **(h)** Gut microbes produce neurotransmitters and influence stress, anxiety, and mood by communication with the brain via the vagus nerve [106–108,115•]. **(i)** Oral biofilms exhibit extensive evidence for host–microbial and microbial–microbial coevolution in biofilm formation [166–169]. **(j)** Gut microbes are critical for the development of the immune system early in life [31,51,52,117]. **(k)** Infants acquire their microbiota via both vertical and horizontal transmission and are subject to environmental influences [28•,36••,37,44••]. **(l)** Traditional and industrialized societies have distinct gut microbiota [53,54,55•,56•,57]; industrialized microbiota are less diverse and lack specific taxa [55•]. **(m)** Gut microbes convert dietary fiber into short chain fatty acids such as butyrate [86••,170], the primary nutrient for colonocytes [80,81•]. **(n)** Gut microbes synthesize B and K vitamins [82,83], catabolize xenobiotics, drugs, and toxins [65], and play key roles in cholesterol and bile acid metabolism [84]. **(o)** Some microbial strains exhibit patterns of genetic variation that mirror human migration histories [125,155,156].

culture-based techniques [22,23]. The advent of Next-Generation Sequencing (NGS) technologies has made microbiome research feasible for the first time, allowing not only large-scale microbial surveys based on the amplification and massively parallel sequencing of taxonomically informative marker genes (metataxonomics), but also detailed community gene inventories (metagenomics) and functional analyses (metatranscriptomics) [10•]. In addition to these technological achievements, NGS has also enabled a rapid expansion of microbial reference genomes available for comparative analysis, and as of 2016 complete reference genomes were available for 1665 bacterial, 3 archaeal, 111 viral, and 1 eukaryotic human-associated taxa (http://hmpdacc.org/reference_genomes/reference_ genomes.php). Increasingly, these reference genomes are not limited to cultured organisms alone, but can be reconstructed directly from metagenomic data [24•]. This approach has yielded some of the first genomic glimpses at 'dark matter' candidate phyla such as TM7 [25], a clade of epibiotic and parasitic bacteria that includes important members of the human oral microbiome [26], but which has proven largely uncultivable to date. Collectively, these developments have allowed us to advance our understanding of the role of the microbiome in human biology and evolution.

Role of the microbiome in human biology and evolution

Microbiome establishment and dispersal

As with any complex biological system, the initial establishment of the microbiome in infants is controlled by a combination of environmental factors and host genetics. Specifically, mode of birth (vaginal delivery vs C-section) plays a significant role in seeding the infant microbiome, with transference of taxa to the infant from maternal vaginal and gut microbiomes in the case of vaginal birth, and skin and environmental microbes in the case of C-sections [27,28•,29,30]. While this results in a significant difference in early microbiome structure, particularly with reduced species richness among C-section infants, the long-term implications are still unknown [31]. Microbial colonization of the placenta in utero may also play a role in microbial seeding [32], but the impact of prenatal microbial exposure is unclear and largely associated with adverse effects [33–35]. Once established, the infant microbiome undergoes a series of microbial succession events, coinciding with changes in diet, and begins to achieve an adult-like profile with the introduction of solid foods [36••,37].

While environmental factors play a major role in the acquisition and structuring of the human microbiome, several studies have now also identified associations between specific microbial taxa and host genotypes, particularly in the human gut [38,39•,40–43]. One such association is between the expression levels of the maternal Fucosyltransferase-2 gene (FUT2) and the establish-