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Microbiomes are Important Key Players in Human Health-Mutualistic Interactions with and between our Microbes

Pedro David[1], Xana Sá-Pinto[2,3] and Teresa Nogueira[1,4]*

[1]*Centre for Ecology, Evolution and Environmental Changes, Evolutionary Ecology of Microorganisms group, Faculty of Sciences, University of Lisbon, Portugal*

[2]*Research Center for Didactics and Technology in Training for Trainers, University of Aveiro, Portugal*

[3]*School of Education, Polytechnic of Porto, Portugal*

[4]*National Institute for Agrarian and Veterinary Research, Laboratory of Bacteriology and Mycology, Oeiras, Portugal*

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***Corresponding author:** Teresa Nogueira, Center for Ecology, Evolution and Environmental Changes, Faculty of Sciences, University of Lisbon, 1749-016 Lisbon, National Institute for Agrarian and Veterinary Research, Av. Da Republica, Quinta do Marquês, 2780-157 Oeiras, Portugal

Abstract

We are surrounded and colonized, from the inside out, by microbes since birth. Most of the bacterial cells that inhabit our body share a commensal and non-pathogenic behaviour. Collectively they are referred to as the human microbiome, a whole bacterial community relying on us as their natural biome. Likewise, we rely on them and on their genomes in order to adapt to the environment. The human gut is an important reservoir of bacteria playing a crucial role in human health. The average microbial diversity of the human gut microbiome has been gradually reducing over time due to the alteration of some cultural practices, together with antibiotics misuse. In order to overcome this problem, medicine has been involved in the development of innovative medical procedures like, for example, stool transplant from a healthy patient to those affected with chronically diarrhoea and bowel disease, to restore microbial diversity. In this article we explore the composition of the human gut microbiome, some of the interactions it has with the human body and its importance to the overall human health.

Keywords: Microbiome; Human Health; Bacterial diversity; Antibiotics; Dysbiosis; Opportunistic infection; Stool Transplantation

Our Microbiome

A history of Intimacy

Close your eyes. Imagine one ecosystem with soft and hard substrates, 100% moist, temperature between 34 and 37ºC all year around and abundant food resources. Imagine a second ecosystem: dry, with significant temperature fluctuations, high UV exposure and a relatively high substrate instability. Now open your eyes and closely observe these ecosystems. No, we are not describing tropical forests or sand deserts, we are talking about you! More specifically we are talking about your mouth (Van Houte, Gibbons, and Pulkkinen 1972) and your hand's skin [1,2], two of the several ecosystems present in your body that harbour a large and diverse community of microbes including bacterial, viral, archeal and fungal species [3]. This community of microbes living in your body includes commensal, mutualistic and even a few (most probably opportunistic) pathogenic species [4] which are referred to by microbiologists as a microbiome [5]. Telling you what microbes live within/on you is not an easy task, as the characterisation of the microbiomes of hundreds of people shows these communities are variable and dependent on factors such as body surface area, gender, age, diet, daily life habits, ethnicity and geography, health status and your own genome [2,3,6]. But whichever microbes you carry, they are for sure affecting your health.

People tend to better know microbes by the diseases they cause, but human microbiomes have been shown to be essential for our health, ensuring certain functions and providing metabolic pathways that complement those encoded by our genome [3,6,7]. We feed them, and they work for us. In fact, at this moment, your microbes are actively regulating the pH of some of your body areas, fighting other (possibly pathogenic) microbes, providing you with resistance to infections, educating and regulating your immune system to avoid or decrease autoimmune diseases and

exaggerated immune responses, and digesting some of the food you ingested and producing nutrients that are essential to you [3,6,7]. Other essential functions of a healthy human microbiome include gene activity regulation, and the differentiation and maturation of some of our organs and tissues [6-8].

The Gut Microbiome and Human Health

Taken together the genomes of the bacteria and viruses residing in the human gut encode 3.3 million genes. These are so essential in supplementing our genome [9] that, in the Nature Magazine number 464 of March 2010, Liping Zhao called "Our Other Genome" to all the genes belonging to the microbes of our microbiome. So how much of you are you and how much of your body functions are ensured by your cells? According to Martin Blaser (a specialist in the human microbiome) from the nearly 30 trillion cells in our bodies, only less than a third is human, and the remaining 70 to 90% are microbial. And approximately 99% of the unique genes in your body are indeed bacterial [10] and these are encoding functions that are essential for your health. As Ed Yong says, "I contain multitudes" [7]. In fact, excluding the vaginal area, reduced species diversity in human microbiomes is usually associated with pathologies [3]. The lack of species that perform some of these essential functions in gut microbiome is associated with obesity, inflammatory bowel disease, types 1 and 2 diabetes, and in skin is associated with atopic dermatitis and psoriasis [3]. But these can also be due to the reduction of species with similar functions in the community (functional redundancy) which may turn microbial communities more susceptible to changes in their environment (such as diet changes, pathogenic infections, medication, or others) and less able to recover from these [3,11].

Yet how have your microbiomes' diversity developed, how does it change over time and what factors affect it? We will now focus on the most studied microbiome, the human gut microbiome, as a model to answer these questions and understand the role and function of our microbiomes. Your gut harbours a wide variety of microbes [12-14], which most probably have been co-existing in a stable equilibrium since your adulthood, and dominated by the phyla Firmicutes, Bacteroidetes and Actinobacteria. An equilibrium is usually defined by the existence and abundance of 3 types of bacteria: *Bacteroides, Prevotella or Ruminococcus*. Each of these bacteria genus defines a different microbiota group, known as an enterotype [15], where the predominant above-mentioned bacteria establish positive interactions with other bacterial groups, and negative interactions with some others, which are thus not favoured and disappear. Although mostly stable, your enterotype can be disturbed by changes in your habits such as when you change your diet, take antibiotic, probiotics, prebiotics and other factors. The good news is it will recover most of the times if these unusual situations are not too prolonged or radical. During the normal development of a human baby, several factors influence the maturation process of the gut microbiome before it finally settles on an enterotype, starting-off immediately after birth.

It's believed that human babies have a sterile gut up until birth and is then immediately colonized by microorganisms originating from the mother. Babies born via a natural birth are first colonized by microbes originating from the mother's vaginal canal and intestines, while infants born via C-section are mainly colonized by microbes originating from the mother's skin and neighboring environments. So, if you were naturally born, you were most probably a baby initially dominated by bacteria such as *Lactobacillus, Prevotella* and *Sneathia*, but if you were a caesarean baby, you were probably initially colonised by *Staphylococcus, Corynebacterium*, and *Propioni* having lower counts of *Bifdobacteria, Escherichia coli*, and *Bacteroides fragilis* and higher *Clostridia, Klebsiella* and *Clostridium* difficile counts [16-21]. If you were a preterm baby, you most probably had a delayed development of your gut microbiome, and were initially colonized predominantly by *Coliforms, Enterococci* and *Bacteroides* [22]. Most of your initial colonizers were facultative anaerobes, like *Streptococci* and *E. coli*, which were then succeeded by *Staphylococcus, Enterococcus* and *Lactobacillus* that contributed to develop an anaerobic environment making your gut available to more bacterial species [23,24].

But your microbiome was also influenced by the type of feeding regime that you went through while baby: breast-feeding, infant milk formulas or a combination of both. These feeding regimes introduce and allow different species to develop thus shaping the microbiome [25,26]. The gradual introduction of solid foods in babies' diet further helps the gut microbiome to mature [27]. During this period of adaptation to the new diet the microbiome is still not stable enough, meaning its bacterial composition can easily change, taking up to 3 years to stabilize [16,28]. Other aspects can affect either the development or the already stabilized gut microbiome. An overweight mother most likely affects her baby microbiome, which ends up having a different bacterial composition when compared to babies of "normal" weight mothers [29]. Prebiotics and probiotics both have similar effects on the gut microbiome, by allowing certain bacteria species to more easily grow or by introducing beneficial bacteria directly in the system [30,31]. Antibiotics, on the other hand, even though they are used to fight off harmful bacteria, they can also affect beneficial species, especially wide spectrum antibiotics [32]. On adult gut microbiomes, the factor that more deeply impacts its composition is diet [26] but, by simply living on different geographical locations, and/or in countries at different levels of development, different people can have different gut microbiome compositions, and extended migrations can permanently change the gut microbiome [33].

According to Martin Blaser, ancient transmission of microbes from mother to child would be: "oral (pre-mastication of food), mammary, through breastfeeding and cutaneous (contact with skin), vaginal (passage through birth channel)". However, modern human practices in industrialized countries - such as: "early-life antibiotics, dental amalgams, bottle feeding, early / extensive bathing and Cesarian section" - has been reducing microbe

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mother to child transmission of the indigenous microbiota, lowering microbial richness of the human microbiome from generation to generation [4,34,35].

The Effect of Antibiotics on Microbial Diversity

Antibiotics kill or stop the growth (proliferation) of microorganisms in a microbiome. Exposure to antibiotics affect different bacteria in different ways, and thus alter the composition of the microbiome through time. In developed countries, humans are continuously exposed to antibiotics, either from medical prescriptions for infections treatment or prophylactic purposes, but also, passively, from the agricultural and livestock maneuvers [36] Antibiotics exert a differential selective pressure on bacteria that populate the intestine as each bacteria has a different susceptibility to antibiotics [37] and can shape its genomic composition and virulence [38] Antibiotic exposure may lead to the extinction of the most susceptible species, and even if the treatment is prolonged or made up of a combination of different antibiotics, it may lead to the extinction of several species, with a concomitant decrease in microbial diversity. The new SimulATe software enables to simulate the effects of antibiotic selective pressure on the dynamics of pathogenic bacterial populations and microbiomes and can be used to models the evolution of bacterial populations and communities inside our body, under distinct scenarios [39].

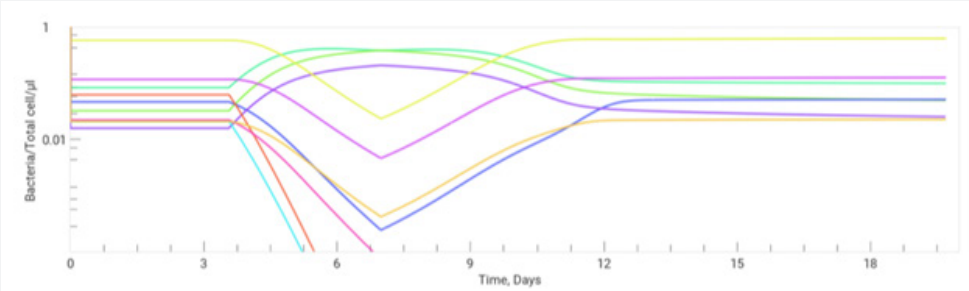

Figure 1: Evolution of the Relative Frequencies of Different Types of Bacteria of a Microbiome. Shortly after Day 3 the Microbiome was Exposed to an Antibiotic for 3 Days.

Figure 1 represents the evolution of the relative frequencies of a hypothetical bacterial community composed of ten different types of bacteria (genus, species, strains…). While under antibiotic therapy, the entire bacterial community is exposed to the antibiotic; those bacteria that are susceptible will decrease in frequency and eventually disappear leading to a disruption of the microbial equilibrium – dysbiosis. After treatment, the microbiome tends to restore its equilibrium. However bacterial diversity can be impaired and unable to restore some physiologic functions of the healthy intestine, by function loss. Since different microorganisms are associated with different metabolic functions, or production of compounds, intestinal physiology may be compromised or impaired. Some bacteria, due to their fitness or ability to produce natural protective antibiotics and stimulate immunity, play a protective role in healthy gut by exerting a colonization resistance to pathogenic bacteria [40,41]. Therefore, the decrease of the diversity and/or on the protective bacterial load in the microbiome allows opportunistic colonization of the intestinal lumen by harmful microorganisms that normally are unable to out compete the dominant organisms. In fact, microbiome dysbiosis increase the susceptibility to pathogens as it can be unable to restrict proliferation of opportunists (usually some less frequent bacterial pathogens) that are able to trigger an infection. It may also lead to other disease states such as: inflammatory bowel disease, ulcerative colitis, rheumatoid arthritis, type 1 diabetes, obesity, atopy and asthma [7,42-44].

Opportunistic Bacterial Infections and Stool Transplantation

In fact, dysbiosis (due to Antibiotic therapy or other causes) is like equilibrium disruptions in other ecosystems. Figure 2 represents a forest ecosystem decimated by a fire (left side of the figure). In this environment, the lack of some key species - like the predator owl – will disrupt the ecosystem equilibrium allowing the proliferation of invading organisms – in this cartoon model example: the rat prey. Reforestation with endogenous species (represented by the water can on the right-hand side of the figure) allows the restoration of the healthy ecosystem that keeps invasive (harmful) species at low, non-threatening levels. *Clostridium sp*. can be one of these harmful opportunistic colonizers of the human gut. They are fastidious growing gram-positive spore-forming bacilli, mostly strict anaerobes. As they share a thick cell wall, they can persist as spores in a vegetative or dormant state when the environmental conditions are unfavourable. The spores are very resistant and thus very difficult to eliminate. They can be the etiological agents of nosocomial infections and are a concern in hospitals and health care facilities [45] as many species of this genus are able to synthesize and release an arsenal of toxins that are very harmful to the human host and can cause human disease such as: botulism, gas gangrene, sepsis or tetanus. One example is *Clostridium difficile* that can naturally colonize the gut microbiome of healthy individuals, yet in very low densities.

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During the last few decades specimens of *C. difficile* has begun to be detected in stool cultures of patients with gastrointestinal disease that have underwent antibiotic therapy [18,19]. Antibiotherapy, with antibiotics such as: ampicillin, clindamycin, fluoroquinolones, and cephalosporins, have been associated with the microbiome disruption (dysbiosis), and overgrowth of *C. difficile*. *C. difficile* can generate an opportunistic infection by producing and releasing two similar toxins: enterotoxin (TcdA) and cytotoxin (TcdB) [46]. They are both responsible for triggering pseudomembranous colitis (PMC), an inflammatory disease that involves damage of the intestinal mucosa, a severe ulceration of the colon, hemorrhagic necrosis, and eventually septicaemia when bacteria enter the bloodstream. This condition can cause septic shock and death [47,48]. They can also code for an arsenal of other virulence factors, like adhesins, that allow them to stick to human cells, and hyaluronidase that dissolves tissues, allowing the progression of the bacteria. Treating PMC may involve long-term antibiotic therapy. But a decade ago, The New York Times reported the case of a woman that was admitted to a Minnesota state hospital in 2008, with severe diarrhoea due to *C. difficile* infection. Her disease was unresponsive to a cocktail of antibiotics, and the woman lost over 12 Kg weight in eight months.

The physician Alexander Khoruts tried a non-canonical new procedure: he asked the husband of the patient to donate a stool sample to be transplanted into his wife intestine. Not only the woman survived the fatal infection, she had recovered overnight and got cured. Two weeks after transplantation a microbiological analysis showed clearly that her husband's bacteria had recolonized and replaced her abnormal gut microbiome. Faecal transplantation has been used for over 50 years, but now it is a very promising and very demanded medical procedure for a myriad of diseases linked to the gut microbiome [49-51]. Since then faecal microbiome transplant ("stool transplant") has been repeatedly used in recurrent debilitated patients [17,18,52,53] .

During faecal microbiome transplantation (FMT) a healthy individual donates its intestinal microbiome to restore the intestinal environment of a diseased individual. A stool sample from a healthy person is blended in a saline solution and surgically injected into recipient patient, either through the nose or mouth into the small bowel, or into the colon by colonoscopy. The new colonizers composed of a healthy community will restore the protective effect against harmful bacteria like Clostridia. This effect is represented in the right part of the cartoon of the Figure 2, by the water can (that symbolizes an enrichment with bacterial strains that restore an equilibrium in a microbiome), and the owl that represents the protective effect of the healthy microbiome against opportunistic pathogens like Clostridia.

Recent studies confirmed that FMT is a useful and valuable tool to treat various chronic gastrointestinal diseases as it increases significantly the species richness [54]. However, although promising, this procedure should be use with precaution. In June 2019 one patient died and another one became seriously ill, following stool transplantation from the same donor. The impacts of microbiome dysbiosis and the effects of faecal transplantations clearly highlight that you are not the only one in charge of your body and your health. You count with the indispensable help of a community of millions of microscopic helpers that complement your own genome and cells. Keeping these community healthy is fundamental for your own health!

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Figure 2: Representation of the Effect of Reforestation and Repopulation of a Burned Forest (where there was Extinction of Species) that Restore Ecosystem Equilibrium and Prevents the Colonization by Harmful Invasive Species.

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