The Long Arm of the Very Small: Human Microbiome and Disease

Rappocciolo E*
Department of Biology and Biochemistry, Birzeit University, Palestine

*Corresponding author: Emilia Rappocciolo, Department of Biology and Biochemistry, Birzeit University, Birzeit, Palestine, Tel: 00970 2 298 2162; E-mail: Erappocciolo@birzeit.edu.

Abstract
It is a well-known fact that we share our body with a large number of prokaryotic cells and viruses that reside on all surfaces of our body and make up what is nowadays mostly referred to as the human microbiota. An estimate of cell numbers puts the ratio prokaryotic to eukaryotic cell count to 10:1 and the size of the microbial genome to 100 times the size of the human genome. While it is in some respect accepted and expected that the presence of the microbiota has a direct effect on the organ in which it resides, it is becoming increasingly evident that they can affect far organs with devastating metabolic and physiological effects on the host. This mini review highlights recent research exploring the impact of the microbiome on far organs and host metabolism.

Keywords: Microbiota; Enterobacteriaceae; Disbyosis; L. rhamnosus; Genotoxins; Obesity; Inflammation

Introduction
The human body is colonized by a large number of microorganisms that have co-existed with us for hundreds of thousands of years. This long term relationship has resulted in an equilibrium that is not only generally neutral to our health and well-being, but most of the time beneficial to us. The microbiota is composed of mostly prokaryotic cells, but also includes some eukaryotic microorganisms, human viruses, plant viruses, and phages [1,2]. Our commensal visitors live on our body surfaces with the greatest number to be found on mucosal surfaces, mostly in the intestine. On mucosal membranes the microbiota interacts very closely with our immune system, establishing constant communication which results in an equilibrium that influences both host immunity and microbial ecology [1]. The presence of gut microbiota is central to the correct anatomical and immunological development in infants [3,4], and microbial dysbiosis has been correlated with disease [5,6] (Figure 1).
Alterations of the microbiome (dysbiosis) lead to an increase in Gram negative species of bacteria, a decrease of Gram positive more beneficial species, a release of genotoxins, and increase in inflammation. These changes can influence the local environment, but also act on far organs to promote disease. It is important to consider that this effect can be amplified via feedback loops (dotted arrows) that can exacerbate changes in the composition of the microbiome.

Intestinal diseases have been linked with alteration in the intestinal microbiota composition. In inflammatory bowel disease (including Chron’s disease and ulcerative colitis) animal model studies have shown that the intestinal microbiota plays a critical role in disease development, as inflammatory bowel disease does not occur under germ-free conditions [7]. Analysis of fecal microbiota consistently reveals less bacterial diversity in ulcerative colitis and Chron’s disease patients compared to controls, with an increased density of adherent bacteria in biopsy samples. As it is often the case with complex diseases it is difficult to determine whether the altered microbiota is the cause or the consequence of the disease, however it is known that segmented filamentous bacteria trigger intestinal inflammatory Th17 cells response which could lead to chronic inflammation [8]. Another local link between the microbiome and intestinal disease concerns colorectal cancer. In a recent article Marchesi et al. hypothesize that Enterobacteriaceae such as Citrobacter, Shigella, Cronobacter, Kuyo vera, Serratia and Salmonella could be responsible for the development of asymptomatic, but chronic, inflammatory response in the colonic mucosa [9]. In addition to the effects of chronic inflammation several Enterobacterial strains produce DNA damaging genotoxins and may thereby actively contribute to the accumulation of mutations that characterize the adenoma-carcinoma sequence [10].

Research is accumulating that implicates the microbiome in disease of organs far from their place of residence and altered host metabolism which could lead to metabolic disorders. The rest of this review focuses on such effects.
Microbiome and Cancer

Cancer results from a multi-step loss of physiological controls in the host cells so that they acquire the ability to invade local tissues and spread widely. Interactions with the microbiome can influence development of cancer through induced inflammation and metabolism.

The intestinal microbiota is one of several factors that can promote the development of local colorectal cancer. Dysbiosis caused by age, antibiotics, xenobiotics, smoking, hormones, and dietary changes, is a well-known factor that can promote the progression to malignancy [11]. It is however difficult to establish whether a change in the microbiota is responsible for promoting cancer, or the tissue physiological changes due to the presence of malignancy induce changes in the composition of the microbiota. It has been recently demonstrated that specific strains of E. coli (phylogroup B2) produce cyclomodulins which are genotoxic and/or modulate cell-cycle progression [12] shifting the paradigm towards a more causative role for the microbiota.

The microbiome is an active parallel organ producing a large and diverse range of metabolic products that can influence host metabolism in organs that are far from the location of the microbiota itself.

The first suggestion of involvement of the intestinal microbiota in the development of breast cancer was derived from results that showed that injections with DMAB (a well-known carcinogen) in germ-free rats resulted in significantly lower cancer development, as compared to conventionalized rats [13].

Plotтел suggests that the influence of the microbiome on the development of breast cancer could be linked directly to metabolic products of the intestinal microbiota. Amongst the many activities of the microbial cells it is possible to identify a functional estrobolome [14] due to bacterial genes whose products can metabolize estrogen. A microbiota that favors the production of enzymes promoting deconjugation of estrogen metabolites, results in re-absorption of free estrogen increasing the total host estrogen burden [14]. There is a direct association between circulating estrogen levels and risk of development of endometrial cancer in post-menopausal women [15]; manipulation of the microbiome to influence specifically the presence of species with beta-glucuronosidase and beta-glucoronide activities could constitute an approach to reduce estrogen related cancer risk [14].

Cancer of the liver is also strongly correlated with conditions of the intestinal microbiota. Alcoholic cirrhosis results in elevated serum content of Gram negative associated endotoxins, and germ-free animals are protected from alcohol induced liver damage [16]. Ethanol-induced hepatic translocation of LPS and Gram-negative bacteria may further synergize with these direct effects in activating the innate immune response [17].

Brain Function and Behavior

The gut microbiota is involved in regulating neurophysiological-governed behaviors through immune, endocrine, and neural pathways. The bidirectional communication between the gut and the brain is known as the microbiota-gut axis and alterations of the microbiota composition can influence central nervous system-related disease and neurological functions [18].

Appetite is regulated by gut hormones produced by enteroendocrine cells located in the intestinal mucosa. Microbial products of fermentation such as acetate and butyrate can be recognized by receptors on the enteroendocrine cells inducing the production of PYY (peptide tyrosine-tyrosine) and GLP-1 (glucagon-like peptide 1) which are known appetite suppressor [19].

Psychiatric disorders have been recognized as causative of changes in the composition of gut microbiota. It has been demonstrated that children with autism spectrum disorders show increased Lactobacillus species, and decreased Bifidobacterium and Prevotella species [20]. It is however proving difficult to demonstrate whether a change in the microbiota can be responsible for the development of neuropsychiatric disorders.

Obesity is associated with increased oxidative stress, which has been correlated with cognitive decline. Transplantation of gut microbiota from High Fat Diet (HFD)-fed mice to mice with depleted microbiota due to antibiotic treatment, disrupts explorative, cognitive, and stereotypical behavior when compared to mice transplanted with microbiota from a control diet [19,21]. Gut microbial metabolism leads to the production of catecholamine, histamine, and other neuroactive mediators that stimulate local enteric nervous system and/or primary afferent fibers [21]. The bacterium Lactobacillus rhamnosus specifically modulates GABA receptors expression reducing stress-induced elevation of corticosterone [22]. Animals fed with L. rhamnosus increase GABA receptor expression in the prefrontal...
cortex and reduce its expression in the amigdala, hippocampus, and LC). Amongst the behavioral changes observed, mice fed with *L. rhamnosus* showed enhanced memory to aversive clues and context [22].

Recent research on HFD mice implicates short-chain fatty acid metabolism by the gut microbiota with the expression of circadian clock genes in hepatocytes [23]. In the presence of gut microbiota, HFD leads to the production of altered microbiome derived metabolic signals which result in disturbed circadian clock rhythm that, in turn, leads to obesity [23].

These interactions between gut and brain could be mediated through Microbiota-Associated Molecular Patterns (MAMPs) and Pattern Recognition Receptors (PPRs). It appears that Gram positive bacteria such as *Lactobacillus* and *Bifidobacterium* have a positive effect in alleviating anxiety [19].

**Metabolic Disease, Obesity, and Diabetes**

The obesity epidemic currently affecting the world is a major reason for increased insulin resistance and type 2 diabetes mellitus. Animal models of obesity have provided many clues on the relationship between diet, microbiome, and diabetes [24]. Several studies are indicating that the microbiome has an important role in regulating fat storage and energy consumption, microbial processing of components of the diet leads to deposition of the extracted energy in host fat deposits [25] and the microbiome could induce a more efficient metabolism to harvest energy via the production of short-chain fatty acids or through pro-inflammatory signals and establishment of chronic inflammation, or a combination of both [26].

Experiments on germ-free mice colonized with gut microbial communities derived from conventionally raised mice result in marked increase of body fat within 10-14 days [25]. The proposed mechanisms for this change are:

a) Microbial digestion of polysaccharides that cannot be digested normally by the host, associated with absorption of monosaccharides and short-chain fatty acids.

b) Conversion by the liver of these products to more complex lipids.

c) Microbial regulation of host genes that promote deposition of lipids into adipocytes (Angiopoietin-like protein 4 – Fiaf) [25].

It has been now proposed that the “obese microbiome” has increased capacity to harvest energy from the diet. Moreover, colonization of germ-free mice with “obese microbiota” produce a greater increase of body fat than colonization with “lean microbiota” [26].

In addition to dysbiosis of the lower intestinal tract, the oral microbiota can also be implicated. Overweight and healthy weight individuals show differences in diversity and abundance of salivary bacteria with *Prevotella* in greater abundance in overweight individuals and *Selenomonas* present only in the overweight population [27].

Obesity related inflammation results in an increase of pro-inflammatory cytokines such as tumor necrosis factor α (TNF-α), which can result in insulin resistance [28]. Gram negative bacteria such as *Bacteroidetes* contain lipopolysaccharide (LPS) which is a known promoter of inflammation. High fat diets tend to reduce the number of Gram positive bacteria and to favor Gram negative colonization of the gut. Increase of *Bifidobacteria* in the gut has been shown to reduce inflammation and improve glucose tolerance [29,30]. The microbiota is therefore responsible for the regulation of both energy harvest and expenditure.

Recent studies based on fecal transplantation in humans, show beneficial alterations in glucose metabolism after lean donor transplantation [31,32].

Type I diabetes is an autoimmune disease characterized by the presence of autoantibody against pancreatic insulin-producing β cells. Gut microbiota can play an important role in regulation of T cells populations in the gut. Non obese diabetic (NOD) mice lacking MyD88 protein (an essential Toll-like receptor signal transducer) don’t develop type 1 diabetes [33,34]. Stools from bio- breeding (BB) diabetes resistant rats contain more probiotic-like bacteria, while *Bacteroides*, *Eubacterium*, and *Ruminococcus* are more prevalent in BB diabetes prone rats [35,36].

**Conclusion**

It is becoming more and more evident that the microbiota that shares our body resources is involved in the homeostasis of many human processes and can have profound effects on far organs and tissues with important repercussions for human health. The next few years will provide important understanding of these mechanisms...
and potentially will provide new therapeutic strategies for treatment of disease.

References


