Journal of Clinical & Cellular Immunology

Rivera-Amill, J Clin Cell Immunol 2014, 5:6
http://dx.doi.org/10.4172/2155-9899.1000e114

Editorial Open Access

The Human Microbiome and the Immune System: An Ever Evolving Understanding

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***Received date:** October 31, 2014, **Accepted date:** November 01, 2014, **Published date:** November 05, 2014*

Editorial

The human body is home to bacteria, archaea, fungi, viruses, protists, and microscopic animals, all of which comprise the microbiome—all the microbes that "share our body space" [1]. The definition of what makes us *human* needs to account for the traits provided by these microorganisms as well as for the fact that we did not have to evolve on our own [2]. Work on the Human Genome Project [3] led to the realization that decoding the human genome would not provide the full picture for understanding human biology, as the microbial communities in/on our bodies by far exceed our own cells in number and gene content [4].

What are the roles of all of the microbes and microbial genes in our bodies? The microbes benefit from a stable habitat—rich in energy sources from the food we ingest—and we in turn claim heat energy from otherwise indigestible compounds such as cellulose. But the interaction between the microbes and their human host is far reaching. The microbiota present at each body site affects numerous biological functions important for maintaining health, whereas the alteration of the microbiota components (dysbiosis) can contribute to disease development. Given the complexity of the human microbiome, identifying and/or interpreting dysbiosis is not trivial. The study of the microbiome is a rapidly evolving area of interest, and a great deal of effort has been invested in understanding the microbial makeup of a healthy individual, that is, to determining what types of microbes are present, and finding out what are they doing. The International Human Microbiome Consortium (IHMC) was constituted in 2005 in order to begin to understand how microbes influence human health and disease [5]. The National Institutes of Health (NIH) joined this international effort by launching the Human Microbiome Project (HMP), an initiative of the NIH Roadmap for Biomedical Research (http://nihroadmap.nih.gov) to examine the normal microbial composition in 4 body sites: the gastrointestinal tract, the mouth, the vagina, and the skin [5,6]. The goals of the HMP are three-fold: 1) to characterize the human microbiome from normal volunteers by using high-throughput technologies; 2) to study several different conditions to determine whether there are associations between changes in the microbiome and health/disease; and 3) to provide a standardized data resource and new technological approaches that can be used by the scientific community. All of the data generated from this effort have been used to define a core microbiome at each body site, denoting the existence of highly specialized niches and interactions between the microbiome and the human tissues [7,8]. An obvious interaction is that of the microbiota with the components of the immune system, both innate and adaptive. The immune system refers to the tissues, cells, and molecules that protect the body against infectious agents. What then determines which microbiota colonizes a particular body site and, in turn, how the microorganisms making up the microbiota help shape our immune system?

The gastrointestinal tract comprises the largest and most complex population of microorganisms, as well as the largest mass of lymphoid tissue, in the body, the gut-associated lymphoid tissue (GALT)—the first line of defense for the intestinal mucosa. As the cellular components of the immune system come into contact with a microorganism, they are faced with assessing whether or not a particular microorganism is beneficial or pathogenic. In addition, the composition of the microbiota itself exerts a reciprocal effect on the immune system. For example, treating animals with different antibiotics often results in the altering of their microbiota profiles, leading to different responses to bacterial infections [9]. On the other hand, the composition of the gut microbiota may also impact the bioavailability and metabolism of the drugs leading to altered disease outcomes [10]. A key experimental advance for unraveling the crosstalk between the microorganisms and their host was the development of gnotobiotic (germ-free, GF) animals [11,12]. The availability of GF animals (no bacteria in the intestine or on other body surfaces)provided important insights into how the microbiota shapes the host immune system. Early studies in the 1960s demonstrated that the cellular and serologic responses in GF mice were slightly delayed and of decreased magnitude and that their macrophages exhibited a decreased digestive capacity as compared to that of conventional mice [13,14]. In terms of the development of the GALT, GF mice display morphological changes resulting from the lack of microbial colonization; compared to mice with microbiota, GF mice have fewer and smaller Peyer's patches, smaller and fewer mesenteric lymph nodes (MLNs), and fewer cellular lamina propria of the small intestine [15,16]. GF animals can be used in the examination of the phenomenon of microbiota colonization and to define the underlying mechanisms of that phenomenon. The gut microbiota provides not only pathogen colonization resistance but also plays a role in immune system–mediated responses. Studies in GF animals have provided evidence of the importance of the gut microbiota in the development a wide range of pathologies. A partial list includes, graft-versus-host disease (GVHD) [17], certain pathologic states resembling both human inflammatory bowel disease (IBD) and ankylosing spondylitis [18-20], colorectal tumorigenesis [21-23], the resistance of the eye to infection [24], obesity [25], and the hypothalamic–pituitary–adrenal axis (HPA) stress response [26], among others. To assess the underlying mechanisms of the human gut microbiota in the development of all of these conditions as well as others, human fecal microbial communities have been transplanted into GF mice using a validated procedure [27]. These *humanized fecal microbiota mice* are instrumental for conducting proof-of-principle trials for examining

the balance of the gut microbiota and the host physiology in the context of environmental and genetic factors. Although not a new therapeutic intervention fecal microbiota transplantation (FMT)—the infusion of a suspension of fecal matter from a healthy individual into the gastrointestinal tract (GI) of a diseased individual—has received much public attention in the treatment and cure of specific diseases. For example, several studies have shown that FMT provides its therapeutic benefit by re-establishing a balanced microbiota in in patients with recurrent *Clostridium difficile* infection (RCDI) [28,29]. To date all the studies have reported remarkable cure rates (>90%) without serious adverse events directly attributable to FMT [30,31]. Benefits of FMT included the restoration of the colonic microbiota to its natural state by replacing missing *Bacteroidetes* and *Firmicutes* species and the resolution of clinical symptoms such as diarrhea, cramping, and urgency [30,31]. Other GI disorders in which FMT has been successfully used include inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS). In the United States, an underestimated 1 to 1.2 million individuals suffer from IBD in a roughly similar distribution between Crohn's disease (CD) and ulcerative colitis (UC) [32].

In the previous issue of this journal, Jin et al. discussed the role of the host–microbe interactions in the development of IBD and the manipulation of the gut microbiota as a clinical therapeutic strategy [33]. Although the etiology of IBD is incompletely understood, a number of contributing factors were discussed, including the role of the microbiome balance (bacteria, viruses, bacteriophages, and fungi) and pathogenic bacteria [33]. An important aspect that also needs to be accounted for is the nature of the microbial and the immune system response interaction during the transition from physiological to tissue-damaging intestinal inflammation that manifests in IBD patients [34]. A recent meta-analysis of FMT as a therapy for inflammatory bowel disease suggests that FMT is generally tolerable and safe [35]. According to the 18 studies (cohort and case) to date that have examined FMT as a primary and adjunctive therapy for IBD, 45% of the patients who participated achieved clinical remission [35]. The lower percentage of clinical remission in FMT-treated patients who had IBD compared to those with RCDI may reflect the complex nature of IBD, and indicates that there is much still to be learned. This observation underlines the importance of understanding the human microbiome, in that doing so should lead to the discovery of disease triggers, novel targets and mechanisms, novel disease interception strategies, and new drugs and diagnostic methods. Currently available modulators of the microbial ecosystem include FMT (described above), prebiotics, probiotics, and antibiotics. However, more refined modulators, such as genetically modified *Lactobacillus*, are being bioengineered offering novel approaches to the prevention and treatment of diseases [36,37]

A look to the near future reveals a number of needs and opportunities. Clearly defining the underlying microbiome–immune system pathways regulating both health and disease processes is important in terms of designing new intervention and therapeutic strategies with improved relevance and efficacy. Advances in sequencing technologies and the development of new tools have let us begin to uncover the dynamics of the microbiome. We must therefore make the most of the renewed interest in the microbiome, which clearly highlights the interests of researchers at many institutions around the world who are teaming up to address the underlying mechanisms of our co-existence with the microbial world.

Acknowledgements

The author would like to acknowledge the editing services of Mr. Bob Ritchie, Ponce Health Sciences University. The project was supported by the National Institutes of Health, NIMHD (G12-MD007579).

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