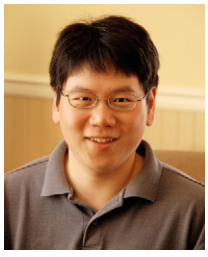
editorial



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Human Microbiome Project—paving the way to a better understanding of ourselves and our microbes

We live in a world dominated by microorganisms. Most of us go about our daily routines without consciously thinking about the impact these microorganisms have, until we become sick. While the study of microbial pathogens has been a major focus since the birth of microbiology, microbes play vital and beneficial roles in many facets of human life and health. With continuing advances in genomic and information technologies, we are starting to unravel the intricate interactions that have co-evolved through time between human beings and our microbial partners (human microbiota) [1]. As new evidence accumulates, we are starting to see that these interactions are complex and cross-linked. Therefore, a holistic approach is needed to understand the role of these microbes in health and disease. The Human Microbiome Project (HMP), an international effort where the mission is to 'generate resources enabling comprehensive characterization of the human microbiota and analysis of its role in human health and disease', provides an important initial step. The project is set to survey five different body sites and to sequence reference microbial genomes from these sites.

Continued advancements in nucleic acid sequencing technologies are facilitating studies of complex microbial communities. In parallel, improvements in computer hardware and developments in the field of bioinformatics allow investigators to process and analyze the ever-increasing amounts of biologic data computationally. Given that the majority of bacteria that reside in communities cannot be isolated in pure culture, it has been necessary to adopt a strategy for the HMP that bypasses the need for cultivation and begins with isolation of DNA directly from an environmental sample. Using molecular markers (e.g. small subunit ribosomal RNA) [2] and random shotgun sequencing of DNA isolated from communities of microorganisms (i.e. the metagenome) [3], we realize that the diversity of the microbial world surpasses our wildest imagination. We have 10^{14} bacteria living on every surface and cavity in the human body. This collection of microbes contains 10 times more cells than the human body, and their collective genomes (the human microbiome) are estimated to contain 100 times more genes than the human genome itself [4]. Our microbiota are highly adaptive. They can evolve rapidly by recombining, duplicating and mutating genes and by acquiring new genes through lateral gene transfer [5]. Changes in the microbiome profile can signal a change in disease states or physiological conditions under observation. New developments in metatranscriptomics, where the mRNA profile of a community can be

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assessed, promise to provide a more accurate view of the functional genes and their relative abundance in a microbiome.

The human microbiota play an important role in human health. In the gut, for example, they contribute to energy balance, to nutrient and drug metabolism, to tissue development, to immune system development and confer protection against enteric pathogens. A landmark study looking at the gut microbiome of two healthy individuals showed that the microbiome is significantly enriched for genes involved in the metabolism of glycans, amino acids and xenobiotics, many of which our own bodies are not capable of metabolizing [3]. Our microbiome also appears to comprise microbes from a limited number of lineages, suggesting an intricate co-evolution between the microbes and us. Jeffrey Gordon's lab has pioneered a series of studies looking at the role of the gut microbiota on obesity in human subjects and gnotobiotic mice (germ-free mice that were given defined microbiome). While the results are too numerous to detail here, the main findings are very exciting. First, a significant difference in the abundance of certain bacterial lineages in obese subjects compared with lean subjects was observed. The 'obese microbiome' appears more efficient at energy harvesting. Moreover, through the manipulation of diet, systematic shifts from one profile to the other occur consistently. When the 'obese microbiome' was introduced into germ-free mice, those mice stored more fat than the mice that received the 'lean microbiome' (for review see [6]). In the most recent study looking at the microbiomes of lean and obese twins and their mothers, the Gordon laboratory showed that, while there is no extensive overlap of microbiota among individuals, there is an early familial influence on the composition of microbiota [7]. Despite these inter-familial and intra-familial variations, the core functions possessed by the gut microbes are remarkably consistent. Certain protein functional categories, such as sugar catabolism, are consistently overrepresented in gut microbiome compared with all bacterial genomes. It appears that different community types of gut microbes are capable of carrying out similar functions in the host. These results provide strong evidence that, by studying the human microbiome, we may ultimately be able to alter our energy balance by introducing prebiotics and probiotics that promote or mimic a 'lean microbiome' or a 'calorie-efficient microbiome' that is individually tailored.

Through the use of NMR and other spectrometry techniques it is now possible to identify metabolic products of the microbiota directly. The field of metabolomics can provide a detailed view on how the gut microbiota process dietary compounds and influence host energy balance and nutrition needs. Moreover, drug metabolism takes place in the presence of the microbiota. A recent paper in which probiotic organisms, Lactobacilli, were fed to mice showed that probiotic treatments altered a wide range of pathways and affected the fat metabolism and bile acid production [8]. The outcome appears to be an increased enterohepatic recycling of bile acids and dietary fats, lowered plasma lipoproteins and stimulation of glycolysis. The profound effects of one probiotic organism highlight the intricate interaction between the metabolome of our gut microbiota and that of ourselves and point to possibilities of manipulating metabolism intentionally through the prescription of probiotics [9]. By combining metagenomics, transcriptomics, proteomic and metabolomics we can interrogate the host–microbe interactions at multiple levels—correlating the genes that are there to their functions.

As we continue to explore the relationship between community structure and function, we must also take into account the fact that the architecture of microbial communities is highly dynamic. In a recent study by Dethlefsen *et al.*, it was shown that a short course of ciprofloxacin in healthy individuals has a significant impact on gut microbiota and affects about one third of all taxa found in the gut [10]. While most taxa rebound to their pretreatment level after four weeks, some taxa failed to return for six months. Interestingly, these subjects suffered no apparent ill effects from the antibiotic administration, suggesting that there may be functional redundancy in the gut microbiota. Nonetheless, these findings suggest that environmental exposures, for example, the food we eat and the drugs and supplements we take, may have cumulative and long-lasting effects on the evolution of our microbiota over our lifetimes. Results such as these in the context of widespread use of broad-spectrum antibiotics suggest that it may be time to rethink our strategies for treating infectious diseases [10]. Up until now, the goal of anti-microbial drug development has been to kill microbes without harming the host. We would argue that our view should be changed. Going forward, we need to consider the design of drugs that target pathogenic microbes while preserving our beneficial microbes. Instead of treating all microbes in the same way, we need to distinguish our partners from our enemies. The efforts of HMP investigators in laboratories around the world will pave the way to improve our understanding of the microbes that are closely associated with us. This new understanding will lead to a more 'enlightened' view of this relationship and new strategies to treat and prevent diseases.

Moving forward, we face some significant challenges and opportunities. The main challenge is to figure out how the enormous genetic diversity can be organized and reduced into meaningful functions. Even with the technology that we currently have, we still cannot sample all the genetic diversity. Therefore, we need to develop guiding principles on how bacteria interact with each other and with us through co-evolution. Scientists are applying sophisticated statistical analyses derived from classical ecological research to study the human-microbiota ecosystem [11]. Also, standards are being developed to store and manage metagenomics data and metadata to facilitate analysis. A Data Analysis and Coordination Center (http://www.hmpdacc.org/) has been tasked to manage the enormous amount of data generated by HMP. As drug and nutrient metabolisms are occurring in the presence of the gut microbiome, improved healthcare can be achieved with improved knowledge of the gut microbiome function. Furthermore, as we get to know our microbiota better, we will improve our ability to culture and study them in the laboratory environment. Using probiotics to alleviate diseases is not new, but tailoring them to individual needs is still unrealized. By gaining a better understanding of our microbiome we, in turn, can understand our own bodies better.

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