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The Human Microbiome and Personalized Medicine

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INTRODUCTION

A detailed understanding of human biology requires not only knowledge of the human genome but also that of the human-related microbial metagenome. The complex and dynamic microbiota has a significant influence on the physiology, nutrition, and immunity of the human body. Disruptions of these human-associated microbial communities or alterations of the close relationships among these microbes and human cells can lead to many health problems. Now, increasing attention is being paid to the connection between the dynamics of the human microbiome and human health, from infectious disease to wound healing, metabolic homeostasis, and oral health. This field is attracting the attention of scientists and physicians worldwide (Bruls and Weissenbach, 2011; Proctor, 2011; Qin et al., 2010; Round and Mazmanian, 2009; Thomas and Ockhuizen, 2012).

The human body, both outside and inside, plays host to innumerable microbes. The microbes in the human body help to protect us from pathogens, digest food, provide nutrient substance, etc. It has been estimated that the human microbiome consists of up to 100 trillion cells, 10-fold the number of human cells. The microbes in the human body encode over 100 times the number of genes compared to genes contained within the human genome.

THE RELATIONSHIP BETWEEN HUMAN MICROBES AND DISEASE

The microbiota have great diversity, and comprise all organisms that are unicellular or live in a colony of unicellular organisms. The microbial world includes bacteria, fungi, archaea, protista, and viruses, which can live in all parts of the biosphere, including soil, water, the ocean floor, and extreme environments such as hot springs, acid mines, or high in the atmosphere; what is more, they are distributed widely throughout the human body.

Human microbes are located, for example, in the oral cavity, genital organs, and skin, and especially in the gut (Figure 14.1).

Human Oral Microbes

The oral cavity is the entry point to the digestive system. It is connected with digestive ducts by the isthmus of fauces and the pharynx. The healthy mouth environment harbors more than 700 bacterial species (Aas et al., 2005). Oral microbes are an important part of the human microbiome, and the unique and diverse microflora, distributed in various oral ecological niches such as the tongue dorsum and the periodontal crevice and pockets, are indispensable. The dynamic ecological balance between the oral microflora and the human body is important to maintain health. And the oral microflora is closely involved in development of oral diseases such as tooth decay (dental
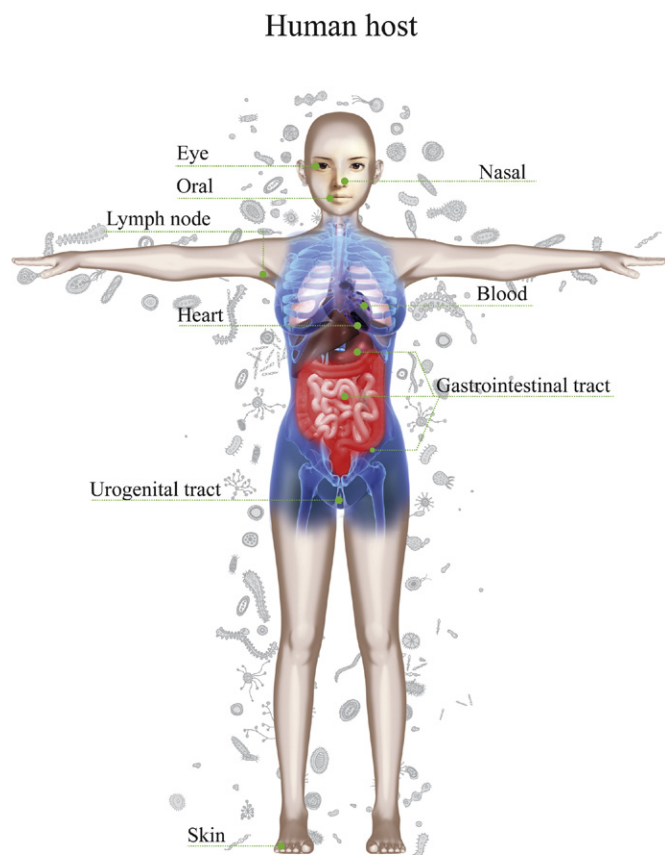
Human host

Eye

Oral

Lymph node

Heart

Nasal

Blood

Gastrointestinal tract

Urogenital tract

Skin

Figure 14.1 The distribution of the human microbiome. Data from http://www.hmpdacc.org.

caries) and gum disease (periodontitis). Maintenance of oral hygiene plays an important part in preventing disease caused by the oral microbiota. Further, understanding the microflora by studying the oral microbiome is of benefit to maintain oral health, avoiding such conditions as caries and periodontal disease, which can be prevented by interfering with the oral microflora (Avila et al., 2009; Zarco et al., 2012).

The microbiota in the mouth includes hundreds of types of microorganisms colonizing a variety of surfaces, of which many grow on tooth surfaces as a biofilm known as dental plaque (Paju and Scannapieco, 2007). Under healthy conditions, the biofilm plays an essential role in resistance to mechanical damage or antibiotic treatment. Biofilm microbes can be targeted by pathogenic microorganisms in oral niches, or under circumstances such as poor oral hygiene. Gram-positive facultative anaerobes (*Streptococcus anginosus* and *Actinomyces naeslundii*) (Ruby and Barbeau, 2002) are the main components of these biofilms, but under conditions of poor hygiene, the percentage of Gram-negative species (for example, *Actinobacillus actinomycetemcomitans*, *Treponema denticola*, *Porphyromonas* spp.) (Raghavendran et al., 2007) in the biofilms increases, and may lead to periodontal inflammation and thus affect negatively the overall health of an individual. Similarly, an increase in the

volume and complexity of biofilms located in the gingival crevice can lead to periodontal disease.

Researchers are also analyzing the relationship between the oral microflora and certain systemic diseases. Clinical studies have shown that microflora in the mouth may be associated with caries, periodontal disease, respiratory infection, and intestinal disease. Invasive dental procedures can lead to bacteremia from the oral cavity, which may subsequently spread to the brain, liver, and lungs. Further, several studies suggest that periodontitis may have an association with systemic diseases such as coronary artery disease and low birth weight, and with distant-site infections such as infective endocarditis (Bahrani-Mougeot et al., 2008). Raghavendran and colleagues (2007) showed that periodontal disease may contribute to the initiation and/or progression of certain lung diseases. In fact, several anaerobic bacteria isolated from infected lungs and respiratory pathogens, such as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Escherichia coli*, have been found in periodontal pockets. These microorganisms have been found to be present in substantial numbers on the teeth in both the institutionalized elderly and intensive care patients.

With the development of higher living standards and longer life spans, people pay more attention to human health management and disease prevention. Improved knowledge of the oral microbiome and the relationship between human health and the oral microbe will play a positive role in maintaining the health of the body as a whole.

Human Gut Microbes

The gut is the part of the alimentary canal extending from the stomach to the anus, and consists of two segments, the small intestine and large intestine, involved in food digestion. Gut microflora participate in intestinal glucose, lipid, and amino acid metabolism, and metabolism of other nutrients essential to health. The intestinal flora is closely involved in the development of host metabolic disease. In the gut, reduction of *Bifidobacterium* and *Lactobacillus* can reduce the ability of fermentation to digest food and thus change metabolism; defects in energy homeostasis can lead to insulin resistance, type 2 diabetes, obesity, and inflammatory bowel diseases. Consequently, widespread attention is now being paid to gut microflora (Ley, 2010; Qin et al., 2010; Round and Mazmanian, 2009).

Some have studied the relationships between gut microflora and disease. Dysbacteriosis, microbial imbalance on or within the body, has been explored by phylogenetic assessment of gut microflora between patients and healthy controls, using 16S ribosomal RNA genes to inventory the various microbes present. This analysis indicated, for example, that the diversity and relative proportion of bacteria of the phylum Firmicutes may be altered in patients who suffer from inflammatory bowel diseases or obesity (Kuehbacher et al., 2008; Ley, 2010; Turnbaugh et al., 2006).

Research on host-intestinal microbes between obese and lean individuals has identified that obesity is associated with phylum-level changes in the microbiota, reduced bacterial
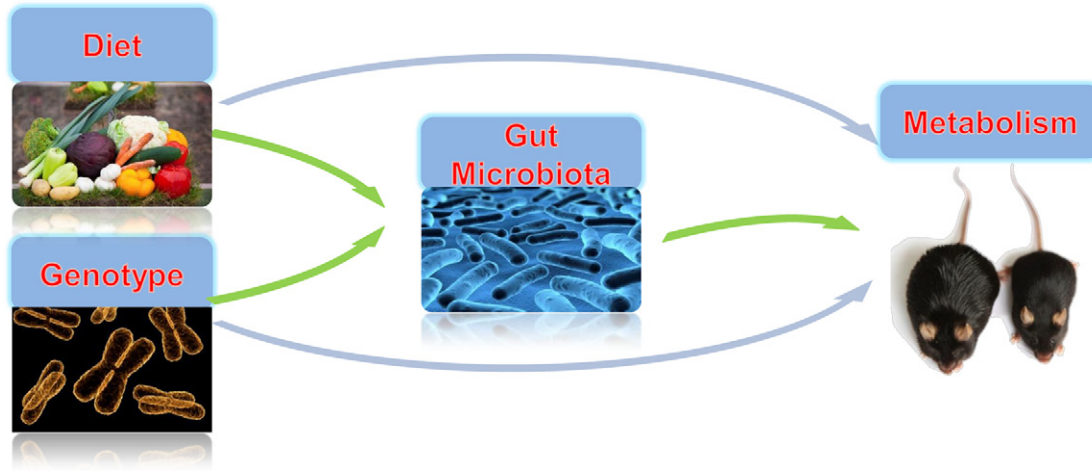
Figure 14.2　Altered host–microbiota interactions in the gut.

diversity, and altered representation of bacterial genes and metabolic pathways. A key study indicated that the gut microbiota act as an additional contributing factor to the pathophysiology of obesity (Turnbaugh et al., 2006). Other studies have also demonstrated an association between obesity and gut microbes (for example, Delzenne and Cani, 2011; Tilg and Kaser, 2011).

Diet and genotype can influence the body metabolism and cause metabolic disturbance, resulting in metabolic diseases such as obesity, diabetes, and gastritis (Figure 14.2). Some research indicates that diet and genotype can influence body metabolism via affecting the gut microbiota, likely mediated through the immune system (Kau et al., 2011). High-fat and high-energy diets lead to a change in the composition of the gut microbiota. Such variation in the gut microbiota influences the body metabolism, leading to, for example, obesity and/or diabetes. One report showed that TLR5 receptor deletion in mice can cause alterations in the composition of gut microbiota and, in turn, influence metabolism through malfunction of the innate immune system (Vijay-Kumar et al., 2010).

Human Skin Microbes

Skin is the soft outer covering of an animal, made up of multiple layers of ectodermal tissue; because it interfaces with the environment, skin plays a key role in absorption, sensation, water loss, and protection against pathogens. The skin is the largest organ of the integumentary system in the human body, on and within which bacteria thrive. One of the largest microbial habitats is the skin surface, which harbors large numbers of bacteria that have important effects on human health. As reviewed recently by Grice and Segre (2011), the skin is a nearly two-square-meter ecosystem comprising a variety of habitats and niches, each harboring its own microflora.

Grice and her colleagues have charted the microbial communities inhabiting the inner elbows of healthy people (Grice et al., 2008). They obtained over 5000 16S rRNA gene sequences, and found that most of these sequences derived from the Proteobacteria division and mainly from the genera *Pseudomonas* and *Janthinobacterium.* They studied 113 operational taxonomic units (OTUs; "phylotypes") and found them to belong to six bacterial divisions, Proteobacteria, Actinobacteria, Firmicutes, Bacteroidetes, Cyanobacteria, and Acidobacteria, that were different in terms of core members from the gut microbiome. Furthermore, this study found that when considering bacterial community membership and structure, interpersonal variation is approximately equal to intrapersonal variation, indicating a low level of individual variation, at least in healthy people. Subsequently, they generated 112,283 near-full-length bacterial 16S gene sequences from samples of 20 diverse skin sites on each of 10 healthy humans, and found that physiologically comparable sites harbor similar bacterial communities (Grice et al., 2009). The complexity and stability of the microbial communities, however, are dependent on the specific characteristics of the skin site (Grice and Segre, 2011).

Recent studies have provided invaluable information about the abundance and types of microbes on the skin, and some studies have tried to address their function. It seems that skin microbes live in peaceful coexistence with the host, but amongst the harmless skin flora, a pathogenic agent is often found.

Staphylococcus epidermidis, a major inhabitant of the skin and mucosa, is the most common clinical isolate from the cutaneous microbiota. Over the past several years, *S. epidermidis* has emerged as a frequent cause of nosocomial infections. Various factors change *S. epidermidis* to an infectious agent in some patients, including drug abusers, those on immunosuppressive therapy, those with acquired immune deficiency syndrome (AIDS), premature neonates, and patients with an indwelling device. *S. epidermidis* infection can be initiated via foreign bodies such as catheters and implants, then cause sepsis, native valve endocarditis, or other subacute or chronic conditions in the patient risk-groups outlined above (Cogen et al., 2008).

Human Generative Organs Microbes

Microbes of the human generative organs mainly colonize the female's vagina and the male's genital tract, and pathogens

may result in generative infection. Infection of the reproductive organs may lead to many diseases, such as inflammation and infertility.

In normal situations, the generative organs are populated by a well-balanced microbe community. Microbes are common in semen from infertile men. Studies have shown that pathogenic bacteria infecting the male generative organ include *E. coli*, anaerobic bacteria, *Streptococcus viridians*, and *Mycobacterium tuberculosis*.

Vaginal bacterial communities are composed of mixtures of diverse species, and the relative abundance of and balance among these species in part determine urogenital health and disease in women (White et al., 2011). It is generally acknowledged that vaginal communities predominated by *Lactobacillus* species are normal and healthy, while communities predominated by other species, such as *Gardnerella vaginalis*, are abnormal and unhealthy, and can cause disease such as bacterial vaginosis (BV).

BV is a common gynecologic disease in women. While slight BV is asymptomatic and benign in some women, it is a common cause of malodorous vaginal discharge for many. More, BV can influence fetal growth and even cause infertility. BV may also induce other diseases, such as genital infection, pelvic infection, and perinephritis. Some studies have found *G. vaginalis* to be implicated in BV, but it has not yet been identified as the cause.

Recent research on BV has reported assessments of bacterial species in women with and without bacterial vaginosis using quantitative polymerase chain reaction (PCR) (Zozaya-Hinchliffe et al., 2010). The results showed that *Lactobacillus* species were predominant in normal vaginal specimens, and that high *L. crispatus* and *L. jensenii* abundance was characteristic of normal specimens, while *L. iners* abundance was high in all categories, including BV. The abundances of all non-*Lactobacillus* species were higher in BV specimens than in normal specimens. *Prevotella* species were prevalent in all specimens, and represented a high percentage of total species in BV specimens.

Human Nasal Microbes

As we know, the nose is the door to breathe air, including some dirt and pathogenic microorganisms. So, the function of the nose is to filter the air and reduce the levels of pathogenic microorganisms; otherwise, the nose, lungs, and other organs would become infected, leading to chronic pharyngitis, chronic tracheitis, and nasosinusitis, and even cause secondary lung infectious disease.

Studies have shown that the nose has a normal microbial environment that doesn't cause disease. The nasal environment is colonized by a temporally stable microbiota, which is distinct from that of other regions of the integument. The nasal microbiota in healthy humans primarily belongs to only two bacterial phyla: Actinobacteria (68%) and Firmicutes (27%). It also contains other phyla such as Proteobacteria, Bacteroidetes, Fusobacteria, Cyanobacteria, Tenericutes and Deinococcus (Frank et al., 2010). Notably, inpatient nasal microbiota includes Firmicutes (71%) and Actinobacteria (20%) at levels that are substantially different from those found in healthy humans (Frank et al., 2010). Firmicutes are significantly more abundant in inpatients compared to healthy adults, whereas Actinobacteria are concomitantly less abundant compared to healthy adults. The increased abundance of Firmicutes is due to an increase in *S. aureus* and *S. epidermidis* (Frank et al., 2010). Studies indicate that microbial competition during colonization of the nares could be exploited to limit *S. aureus* colonization (Frank et al., 2010).

ADVANCED TECHNOLOGIES FOR THE STUDY OF THE HUMAN MICROBIOME

The understanding of the human microbiome relies mainly on the development of new metagenomic approaches to study the diverse genomic content of the microbiota. The traditional microbiological study of human microflora, its complexity and genetic polymorphism, mainly based on laboratory culture technology, has serious deficiencies, for it is well known that less than 1% of microbes can be incubated in the laboratory. Now, modern biological technology based on DNA analysis of microbial communities by direct genomic analysis bypasses separation and cultivation of microbial species, and can provide a more comprehensive and, in principle, bias-free approach to the study and understanding of the human microflora (Kuczynski et al., 2010; Qin et al., 2010).

In the early days of the metagenomics period, the gene for the small subunit of the ribosomal RNA (SSU rRNA) was often studied, because of the feasibility of obtaining data useful for taxonomic classification and exploration of diversity. Compared with earlier methods, such as denaturing gradient gel electrophoresis and oligonucleotide chips, the emerging high-throughput sequencing technologies (see Chapter 7) have advantages for rRNA analysis in metagenomics. For example, they make it possible to determine an accurate taxonomic assignment, even for low-abundance species, and have the potential to identify novel operational taxonomic units. Benefiting from rRNA gene sequencing, many published studies have broadened our understanding of the taxonomic structure of the natural microbial world.

However, supported by *in vitro* evidence, analysis of a single phylogenetically informative gene is limited, and unable to explain all functions and metabolism of a bacterial species. Thus, as sequencing technology and bioinformatics tools advance, a whole-genome shotgun (WGS) strategy presents a powerful alternative to rRNA sequencing and is becoming popular in metagenomics study, promising to provide the complete functional repertories of bacterial genomes. Genomic DNA was randomly broken up into small fragments, which are sequenced to obtain reads. Multiple reads for the target DNA are obtained by performing amplification and sequencing. Then the reads were assembled into continuous sequences

by computer programs. DNA reads generated by this type of metagenomic sequencing can be assembled into longer composite sequences by reads overlapping or even complete genomes, and could also be considered directly as environmental gene tags (EGTs), the short sequences from the DNA of microbial communities that contain fragments of functional genes. While such a vast amount of information can be produced from a metagenomic sample by WGS sequencing, suitable bioinformatics tools are still needed to, for example, reconstruct bacterial genomes, explore taxonomic diversity genome-wide, annotate genomes (and community metagenomes) in terms of functional composition, and carry out association studies between microbiome diversity and phenotypes.

The above has described metagenomics studies based on DNA sequencing. Besides DNA-level analysis, however, a comprehensive understanding of a natural microbial community also requires an RNA-level analysis (meta-transcriptomics), a protein-level analysis (meta-proteomics) and a metabolite-level analysis (meta-metabolomics). In human microbiome studies, applied by an integration of these various technologies, a correlation model between the biology of microbiomes and human health will be constructed, revealing mechanisms of host×microbe crosstalk that contribute to our phenotypes in health or disease.

INTERNATIONAL METAGENOME PROJECTS

Microbes are the class of organisms most intimately connected to ourselves, as diseases such as severe acute respiratory syndrome (SARS), tetanus, typhoid fever, diphtheria, syphilis, and Hansen's disease, caused by diverse pathogens, illustrate. To systemically study a microbial community and elucidate the mechanisms linking human health and the human microbiome, a variety of international efforts have launched the microbiome era. Many projects have been funded to document and explore the human microbiome, including the Human Microbiome Database (HOMD), the Human Microbiome Project (HMP) (Proctor, 2011), and MetaHIT.

The HOMD provides two primary types of information – taxonomic and genomic – and has detailed records on species, metabolism, and pathogenic capacity of oral microbes. HOMD plans to provide the scientific community with comprehensive information on the approximately 600 prokaryotic species that are present in the human oral cavity. It will become an important tool for searching for information on oral microbes, forming new scientific hypotheses, and eventually developing improved treatment methods to combat oral diseases.

The HMP, funded as an initiative of the US National Institutes of Health (NIH) Roadmap for Biomedical Research, is a multi-component community resource (Peterson et al., 2009). The HMP plans to sequence, or collect from publicly available sources, a total of 3000 reference genomes isolated from all human body sites that are currently known to harbor large numbers of microbiota that have been shown to have a large impact on human health, in order to characterize the human microbiome more fully (Proctor, 2011). In order to explore the relationships between the human microbiome and health/disease, HMP intends to study several different medical conditions and provide both a standardized data resource and new technology for such studies. All in all, the ultimate objective of the HMP is to prove that humans can improve their health through optimizing the human microbiome. In May 2010, HMP announced a catalog of reference genomes from the human microbiome, including 365 sequenced genomes that were publicly available (Human Microbiome Jumpstart Reference Strains Consortium, 2010).

The MetaHIT project started in 2008, with the strategic aim of fully characterizing the human microbial metagenome. MetaHIT focuses on the intestine, in which the microbial population is at a high density with high variability, and plays a major role in human health. The project aims to create a complete reference gene and genome set of human gut microbes by using high-throughput sequencing technology. Based on this gene set, they plan to develop tools to study variation in human gut microbes, search for associations between gut microbiota and their genes and health and disease, and then study the function of microbial genes correlated with disease. The MetaHIT project will create a database to store and organize the information generated within the project, and create the bioinformatics tools to carry out the meta-analysis.

PERSONALIZED MEDICINE TARGETING OUR "OTHER" GENOME

The same treatment in different individuals may result in different therapeutic effects, drug therapy may fail in some patients or populations, and some patients may have serious side effects. So, therapy is often modified by "trial and error," and this represents an opportunity for personalized medicine, using a person's individual genetic information to improve disease treatment, diagnosis, and prevention.

As we all know, the bacterial genes in our bodies are 150-fold more abundant than our own genes. It will be necessary – and, one predicts, useful – to personalized medicine to take into account this human microbial gene catalog that is our "other" genome.

Diagnostics and Prognostics Based on Our Other Genome

Many chronic diseases have been steadily increasing over the past 50 years in European populations. To cite just a few examples, persons with inflammatory bowel diseases and functional disorders of the gastrointestinal tract make up a considerable proportion of the population. And there are low-grade inflammatory components in obesity, metabolic syndrome, diabetes, and cardiovascular disease. What's more,

chronic disorders, such as allergy, multiple sclerosis, celiac disease, and non-alcoholic fatty liver disease, depend on two factors: one's genetic susceptibility (i.e., polymorphism of the human genome) and exposure to triggering environmental factors, where dysbiosis of the intestinal ecosystem (variation of the metagenome) is being considered as a main risk factor. Consequently, the necessary diagnostic or prognostic tools could be translated based on a two-pronged approach. One is the large-scale exploration of associations between gut microbes and chronic diseases, and the other is the development of varied technologies.

Improvement of Treatment of Disease

To different individuals, medications have different efficacies. There are well-known examples. Anti-tumor necrosis factor (anti-TNF) treatment for Crohn's disease is effective in only two-thirds of patients. Tetracycline, used for common skin diseases such as acne vulgaris and rosacea, is metabolized by cytochrome P450 (CYP450), but can also be associated with serious side effects. In treatment of obesity, there are few valid and harmless treatments, the most common being diet and exercise. However, the effectiveness of these varies substantially between individuals, exemplifying that differentiating responders and non-responders is a major challenge for personalized medicine.

To solve this issue, treatment and drugs developed specifically for individuals are required. Deep metagenomic studies have indicated that individuals could be classified into groups, based on their intestinal microbial communities, named enterotypes. Several steps might be considered:

- Comparing microbiota of patients who either respond or do not respond to a particular treatment
- Developing classification methods to stratify individuals into groups based on enterotypes
- Selecting the most useful treatment for each different individual.

In order to re-establish the balance of the microbial communities that are changed by disease, the capacity to intervene needs to be developed. Three broad strategies might be considered to modulate the microbiota.

- Promoting the beneficial microbes, using prebiotics, probiotics, and so on, which would require help from the pharmaceutical and food industries
- Inhibiting the "negative" microbes, which would require a "soft" antibiotic
- Fecal transplantation, which has been used for *Clostridium difficile* treatments, opening biobanking possibilities in anticipation of later self-transplantation, analogous to storing individual stem cells.

We first need to comprehend the molecular and cellular mechanisms that condition and define interactions between our microbes and our body. Then we would have the capacity to treat disease in a reasonable way. Understanding the correlations between disease and microbes means not only knowledge of the causal relations between their presence and their effects, but also a full understanding of their molecular mechanisms. This will require functional studies, analogous in scope to the just-beginning functional annotation of the human genome. We will need to study the characterization of healthy and sick individuals at the levels of the genome, transcriptome, and microbiome, identifying the related signaling pathways of the interacting molecules. We can draw support from animal models to study beneficial and harmful microbial species and the relevant host responses.

Recently, people around the world have begun to pay close attention to the ideal of personalized medicine. Personalized medicine will be based on the capacity to generate, store, organize, and interpret DNA sequence information – not just of an individual's own human genome, but also his or her microbiome. The prospect of personalized medicine is bright, but one shouldn't underestimate the challenges of developing adequate sequence capacity and the bioinformatic and computational tools needed to make sense of those data.

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RECOMMENDED RESOURCES

The Human Microbiome Database (HOMD)
http://www.homd.org
The Human Microbiome Project (HMP)
http://hmpdacc.org

The MetaHIT project
http://www.metahit.eu/