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EDITORIAL

Translational aspects of the microbiome—to be exploited

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The scope of Cell Biology and Toxicology had been opened towards translational research as was discussed in the editorial of the Xiandong Wang (Gu and Wang 2016). Translational research supports the close collaboration of different specialties ranging from basic science research to clinical studies. That approach may shorten the time it takes for developing new treatment possibilities or schemes. To better understand the complexity of such methodology, hereby we review an exciting field, the microbiome—from a translational point of view (Fig. 1).

The human body harbors symbiotic, commensal and pathogenic bacteria in enormous numbers. These microbes live in the cavities (e.g., gut, genitals, or airways) or on the surface of the human body, the skin. The ensemble of the microbes in an organism is referred as the normal flora. Changes in the composition of the normal flora, the invasion or over-proliferation of pathogenic bacteria had long been associated with diseases (e.g., *Helicobacter pylori* infection of the stomach) and had been translated already to the everyday clinical practice. Recent developments in research technology have vastly increased our knowledge on the "normal flora," Next generation high-throughput sequencing experiments have demonstrated that there are more bacterial species in the gut than it was known from classical microbiological cultures. These studies have identified numerous new bacterial species, among them several obligatory anaerobic strains that are impossible to culture. The ensemble of microbes in a compartment (e.g., gut or airways), identified by sequencing, is referred as the microbiome or microbiota. Due to the abundance and variance of microbes, the overall size of the genomes of these organisms exceeds that of the human genome, extending vastly the variability of genes in a compartment. Therefore, several authors consider the microbiome as an additional organ and recently proposed to consider the ensemble of the human and microbial genomes present in one human being the "metagenome."

There is an intricate bidirectional interaction between the host and the microbiome. The composition of the microbiome is governed by the behavior (e.g., hygiene), feeding, metabolism, and immunological characteristics of the host. While the microbiome influences host metabolism, immune reactions, and behavior through (1) releasing its own metabolites (e.g., short chain fatty acids), (2) modifying the metabolites of the host (e.g., secondary bile acids, primary amines, metabolites of aromatic amino acids (e.g., Trp), lactate, pyruvate, redox-modified sex steroids or polyphenols), (3) metabolizing nutrients (e.g., dietary fibers), or (4) synthesizing vitamins and

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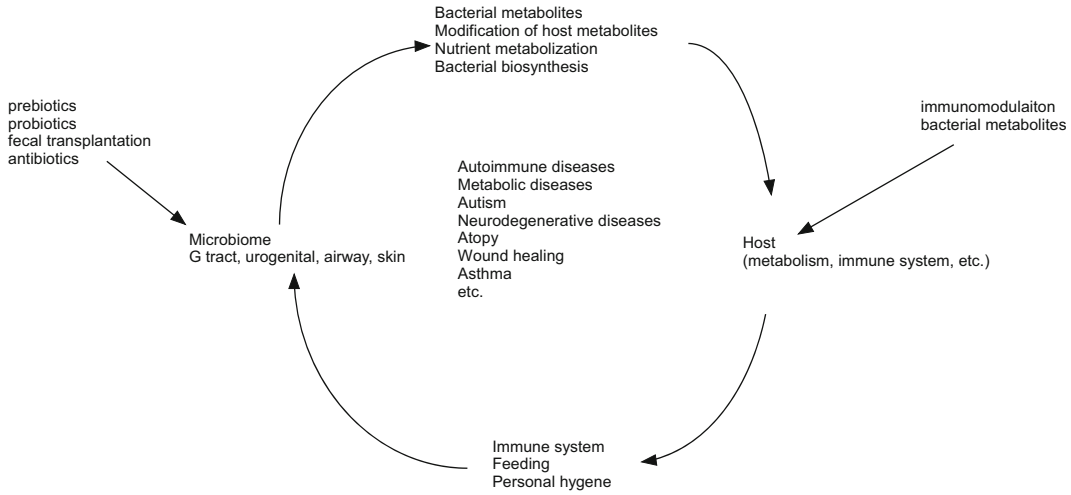

Fig. 1 The bidirectional fashion of the microbiome-host interaction

(digestive) enzymes (Donia and Fischbach 2015; Li and Chiang 2014). These bioactive substances (metabolites) act through various pathways that involve the modification of gene expression (e.g., activation of histone deacetylases and other lipid-mediated transcription factors) or the modulation of signal transduction in the host.

In disease, the composition of the microbiome complexity (richness) often decreases or shows characteristic changes (Le Chatelier et al. 2013). Probably the oldest observation in conjunction with microbiome changes was the identification of the relationship between the oral microbiome, oral hygiene, and cardiovascular diseases; bad oral hygiene increases the risk for cardiovascular catastrophes. In fact, there is a surprisingly large number of diseases that are associated with changes in the microbiome.

The gastrointestinal (GI) tract innate immune system is the first layer of communication between the gut microbiome and the rest of the body. The main role of it is to provide a physical barrier with the possibility of a two-way communication. This communication is promoted by intestinal epithelial cells including absorptive enterocytes, mucus-producing goblet cells, hormone-producing enteroendocrine cells, and antimicrobial peptide- and lectin-producing Paneth cells (Ignacio et al. 2016). The selective permeability allows the absorption of both nutrients and bacterial metabolites from the gut. The uptake of bacterial metabolites contribute to immune responses by providing pathogen-associated molecular patterns to pattern recognition receptors such as toll-like receptors, nucleotide-binding domain leucine-rich repeat-containing receptors, RIG-I like receptors, C-type lectin family receptors, and AIM-2-like receptors (Ignacio et al. 2016). Consequent macrophage and dendritic cell activation induces cytokine production which in turn leads to inflammatory Th17 or regulatory T cell activation and may ultimately result in T cell dependent and independent IgA class-switching responses (Rescigno 2010; Farache el al. 2013; Schulz and Pabst 2013). Through this two-way communication, the microbiome composition affects the severity of autoimmune diseases like inflammatory bowel diseases (IBLD), asthma, rheumatoid arthritis, and type I diabetes (Arpaia et al. 2013; Trompette et al. 2014). Microbiome composition seems to have an intricate connection with autism and neurodegenerative illnesses such as Alzheimer's disease (Hsiao et al. 2013; Macfabe 2013). In addition, microbiome-derived metabolites impact the mitochondrial metabolism of the host and alter susceptibility to metabolic diseases including obesity, insulin resistance, type II diabetes, and gestational diabetes (Le Chatelier et al. 2013). The microbiome represent the tumor microenvironment for gastrointestinal tumors; among them, the best studied is the colorectal carcinoma. Characteristic microbiome changes are not only associated with tumorigenesis, tumor promotion, and the severity of the disease, but the actual composition of the gut microbial community affects the effectivity of chemotherapy too. There are emerging fields such as the study of the skin microbiome (e.g., atopy, chronic wounds) (Wolcott et al. 2015), the airway (respiratory) microbiome (Rogers et al. 2015), aging or pregnancy, and perinatal development (Martinez 2014; Prince et al. 2014).

Importantly, due to the bidirectional fashion of the microbiome-host interaction, changes in microbiome are not only passive markers of disease but seems to play an active role too. Therefore, it is also possible to manage diseases through modifying microbiome (Holmes et al. 2012) that confers a strong and widespread translational potential to microbiome modification strategies. The application of different prebiotics or probiotics, even in the form of functional foodstuffs, are long known possibilities. It is also common knowledge that antibiotics modify the composition of the microbiome, generally the variability of the flora reduces upon antibiotic usage. A novel method that is applied for the treatment of recurrent *Clostridium difficile* infection is called fecal transplantation (Smits et al. 2013). In that process, the microbiome of the diseased individual is replaced by the fecal microbiome of a healthy individual (usually a family member). The introduction of the fresh flora enables the regrowth of the original flora. On the long run, the selective addition or transplantation of bacterial strains or the construction of healthy feces banks may be viable approaches. Changes in microbiome, absolute or relative abundance of a species or a group of species, can be also used as a biomarker of a disease that can be retrieved in a truly noninvasive fashion.

As discussed earlier, bacterial metabolites are relatively unexplored and represent huge translational potential. These metabolites may connect different microbial compartments or between tissues distant to the microbiome. The identification and assessment of bacterial metabolites may develop into a very valued field, as bacterial metabolites may represent a novel class of drug candidates or disease biomarkers (Donia and Fischbach 2015; Li and Chiang 2014).

On the top of that, there are emerging fields for applied and basic research that will profoundly influence our understanding of the host-microbiome relations. The involvement of the immune system needs to be better defined and the effects of immunomodulatory drugs, immune deficiency to microbiome and bacterial metabolome composition could be also be better understood and exploited. The microbiome has an indispensable role in infection control, not only bacterial, but viral, retroviral infections are mediated by the composition of the microbiome (Kane et al. 2011) that is another feature with practical applicability. Differences in microbiome composition brings about differences in the secreted enzyme composition (e.g., gut microbiome contributes to the digestive enzyme pool of the intestine) and biosynthetic activity (a trivial example is vitamin K synthesis in the large intestine) that may lead to individual differences in nutrient digestion, drug metabolism, and many other idiosyncratic features. Along the same line, we should change our current paradigms and imagine the microbiome as a warehouse of bioactive metabolites. Taken together, microbiome studies and inventions will surely impact on personalized medicine and human nutrition.

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