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EDITORIAL

Human Gut Microbiome Researches Over the Last Decade: Current Challenges and Future Directions

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Over the last decade, significant progress has been made in understanding the evolutionary, ecological, and metabolic significance of the gut microbiota for human health. This significant progress owes a considerable debt to the consecutive publication of two seminal research papers originating from pivotal research initiatives: METAgenomics of the Human Intestinal Tract (MetaHIT) (Qin et al. 2010) and Human Microbiome Project (HMP) (Human Microbiome Project 2012).

From an evolutionary and ecological standpoint, these tiny gut microorganisms have forged intricate interactions with their hosts, including humans (Grieneisen et al. 2021; Suzuki et al. 2022). Over millions of years of coevolution, since their colonization of terrestrial ecosystems (Wu et al. 2014), they have become integral to various facets of our health, nourishment, and overall well-being. Their contributions span a broad spectrum, encompassing functions such as immune system maintenance, metabolic regulation, behavior modulation, and even influencing the aging process (Rook et al. 2017). Consequently, the gut microbiome is increasingly acknowledged as a novel 'metabolic organ' (Clarke et al. 2014). This label challenges conventional notions, owing to the gut microbiota's inherent adaptability in navigating the dynamic physiological, biochemical, and nutritional landscape within the intestinal environment. A compelling illustration of this adaptability is the transfer of genes encoding porphyranases—a pivotal enzyme involved in the degradation of polysaccharide porphyran, a significant nutritional component of seaweeds—from marine bacteria to the gut microbiota of the Japanese population (Hehemann et al. 2010).

Despite the rapid advances in gut microbiome research, there remain many challenges that need to be addressed. This issue of *Phenomics* focuses on eight key challenges (Fig. 1) that we are currently facing, with the aim of shedding light on future research directions:

(1) **Defining the healthy and core gut microbiome**: The gut microbiome has attracted increasing interest in revealing its composition, function, and dynamics, as well as the factors that affect its diversity and stability, such as diet, medications, genetics and the circadian clock (Wu et al. 2015). However, there is still much to learn about the healthy and core gut microbiome, including its components, spatiotemporal distribution, variability across individuals and populations, the roles of keystone species and guilds from an ecological perspective, and the existence and evolutionary implications of enterotypes. Longitudinal studies tracking the microbiome over time in healthy individuals will be likely to provide insight into what constitutes a healthy gut microbiome and how it varies over time. Additionally, advanced analytical tools and methods are needed to accurately identify and quantify microbial taxa and functional pathways, as well as to explore the interactions and relationships between them.

(2) **Unveiling bacterial strain differences and functional diversity**: Gut bacteria exhibit an extensive array of strain disparities and functional diversification (Van

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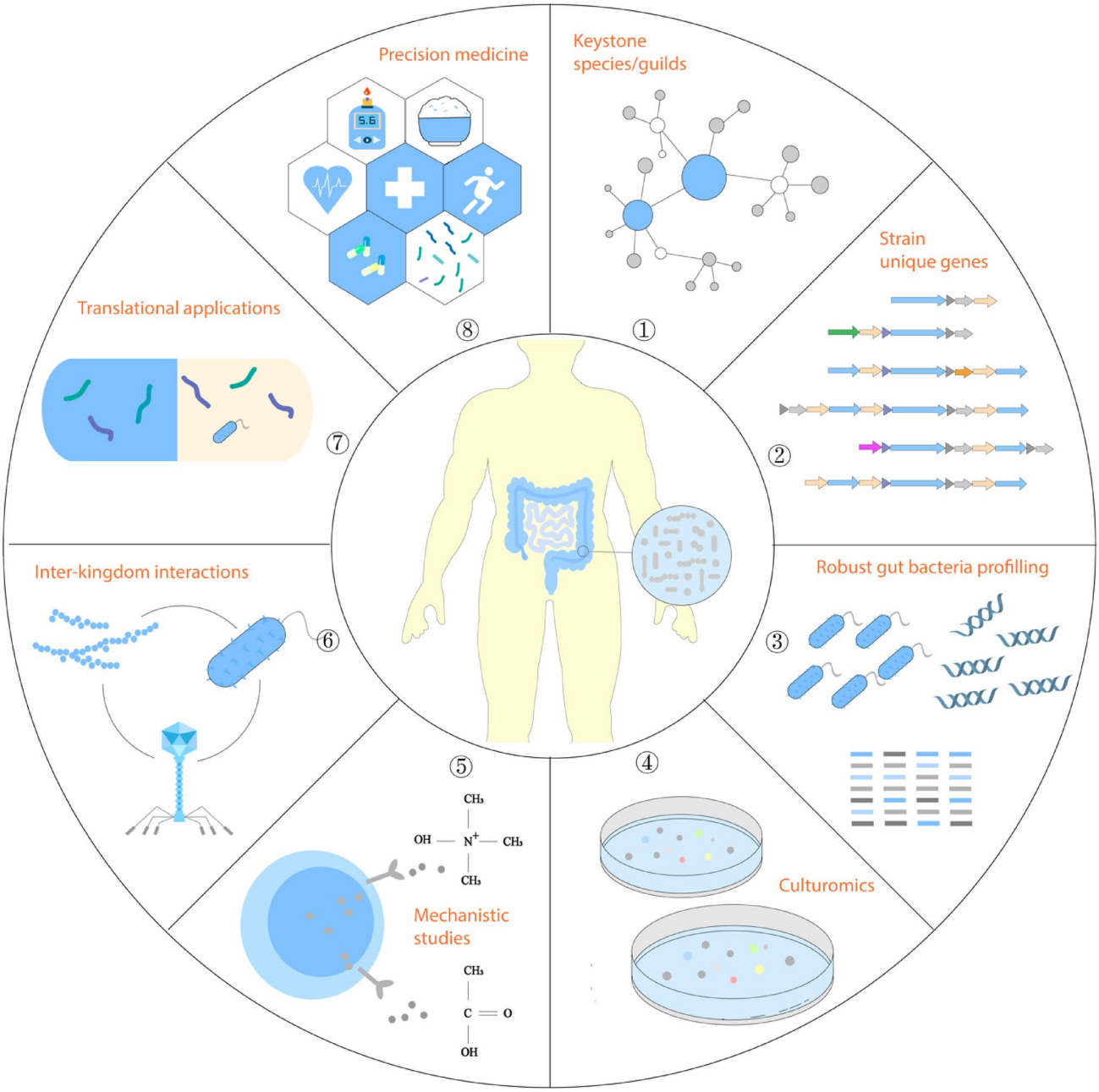

Fig. 1 Eight selected challenges we are facing in human gut microbiome researches. ① Defining the healthy and core gut microbiome; ② Unveiling bacterial strain differences and functional diversity; ③ Robust gut bacteria profiling: DNA and RNA; ④ Culturing the 'yet-unculturable'; ⑤ From association to causal studies; ⑥ From intra- to inter-kingdom interactions; ⑦ From bench to bedside; ⑧ From microbiome to phenome and precision medicine

Rossum et al. 2020). This arises from the presence of limited essential genes or housekeeping genes, countered by a prevalence of accessory genes, mobile elements, single-nucleotide polymorphisms (SNPs), and other structural variations (Greenblum et al. 2015; Zeevi et al. 2019). These complexities pose challenges in extrapolating findings across diverse populations and disease conditions. A case in point is elucidated in a study conducted by Richard A. Flavell and his team, which revealed that only IgA-coating isolates of *Bacteroides fragilis* affect inflammatory bowel disease in mice, not IgA-negative isolates that differ in genetic components despite the fact that those isolates belong to the same species (Palm et al. 2014). Profiling bacterial strains has even leveraged the utility of SNPs (Luo et al. 2015). This underscores the imperative for comparative genomics and pangenomics analysis,

supplementing traditional metagenomics approaches. Furthermore, the intricate investigation of potential roles played by specific genes within a complex microbiome necessitates a synergy of computational analysis and genetic manipulation (Jin et al. 2022).

(3) **Robust gut bacteria profiling: DNA and RNA**: Discrepancies in the relationship between gut microbiota and disease may stem from divergent approaches employed to quantify DNA abundances and growth rates. Tal Korem et al. demonstrated that associations between gut bacteria and type 2 diabetes (T2D) incidence differed based on whether relative DNA abundances or a novel computational pipeline reflecting bacterial growth rates were utilized, with certain exceptions (Korem et al. 2015). Likewise, variations in identifying shifts within the gut microbiota between Crohn's disease patients and healthy controls were evident for genera like *Bacteroides* and *Prevotella* when employing different techniques, including relative DNA abundances or a quantitative microbiome profiling workflow integrating flow cytometric cell enumeration (Vandeputte et al. 2017). Furthermore, robust profiling methods are necessary for both metatranscriptome and metagenome analyses, given the metatranscriptome's heightened temporal dynamics and context sensitivity (as evident from the observation that only 44% of prevalent metagenomic potential being actively transcribed in human fecal samples) (Abu-Ali et al. 2018), potentially yielding stronger associations with specific health outcomes or lifestyle influences.

(4) **Culturing the 'yet-unculturable'**: While culture-independent, genomics approaches have revolutionized our understanding of the role of the gut microbiome in human health and disease, they are not without limitations, particularly when conducting mechanistic studies. "Yet-unculturable bacteria will eventually be cultured" as once suggested by Ruishen Jiao (1918–2009, Chinese Microbiologist). Emergence and development of culturomics since its first reported application in 2012 is gradually proving his words to be true (Lagier et al. 2018). Culturomics employs high-throughput sequencing and multiple culturing conditions and represents the rebirth of culture in microbiology. Recent advances in this field have enabled the identification of hundreds of previously uncultured and thus novel bacterial species from the gut (Lagier et al. 2016; Liu et al. 2021; Zou et al. 2019). Using a combination of automation and machine learning-guided strain prediction, Harris Wang and his team have made significant progress in the rapid isolation of microbes of interest (Huang et al. 2023). However, culturing, which remains the mainstay of culturomics, largely relies on the development of new complex media (Singh et al. 2013). Further integration of longitudinal multi-omics data could even enable mechanistic microbiome researches (Poyet et al. 2019). By shedding light on the microbial darkness of the gut ecosystem, we can gain a better understanding of the intricate reciprocal interactions between these microbes and their hosts.

(5) **From association to causal studies**: Microbiome-wide association studies are crucial for identifying associations between the gut microbiota and human health and diseases. However, to establish causality, these studies must be combined with mechanistic research and human clinical trials, as suggested by many researchers (Chaudhari et al. 2021; Tremaroli and Backhed 2012; Zhao 2013). The importance of moving to causal studies is evident, as many previously identified gut microbial signatures related to T2D were later found to be confounded by medications, particularly glucose-lowering metformin (Forslund et al. 2015). The impact of metformin on gut microbiota has been demonstrated both in vitro and in vivo (Sun et al. 2018; Wu et al. 2017). Similarly, diet can cause rapid shifts in gut microbial composition and function within 24 h (David et al. 2014; Mardinoglu et al. 2018). Furthermore, regional variation may limit the applicability of microbiome-based diagnostic models for metabolic diseases (He et al. 2018). Therefore, disease-associated microbial biomarkers need to be disentangled from a range of confounding factors and mechanistically linked to disease phenotypes and/or host targets termed as the "Gut-X" axes. One example is the identification of a proatherosclerotic species trimethylamine-N-oxide (TMAO) and its heightened cardiovascular disease risk, a scientific research journey that spans over the last 10 years, from Stanley L. Hazen and colleagues (Buffa et al. 2022; Koeth et al. 2013; Roberts et al. 2018; Skye et al. 2018; Tang et al. 2013; Wang et al. 2011, 2015; Zhu et al. 2016). In brief, they have discovered that TMAO, which is a host-microbe co-metabolite resulted from a series of metaorganismal pathways from dietary choline/carnitine/γ-butyrobetaine to trimethylamine (TMA), and then to TMAO, can accelerate atherosclerotic heart disease by enhancing foam cell formation and platelet responsiveness (Koeth et al. 2013; Skye et al. 2018; Tang et al. 2013; Wang et al. 2011; Zhu et al. 2016). In support, this effect can be reversed by inhibiting microbial TMA lyase, responsible for generating TMA in gut microbes (Roberts et al. 2018; Wang et al. 2015). However, TMAO production is also regulated by the gut redox environment (Yoo et al. 2021) and is thus likely modulated by many redox-regulating agents, requiring cautious interpretation of TMAO's role in different disease phenotypes. Improved techniques for studying host-microbe interactions at both the molecular and cellular levels will be important for unraveling the mechanisms by which the gut microbiome affects human health.

(6) **From intra- to inter-kingdom interactions**: Metabolic cross-feeding is common among the gut bacteria and has even been suggested as a new strategy for development of the next-generation probiotics (Khan et al. 2023). Still research on the associations between gut microorganisms

and human health is evolving from a narrow focus on bacteria-bacteria interactions to a broader consideration of inter-kingdom interactions among bacteria, archaea, viruses, and fungi. This shift aims to improve our understanding of the ecology of the microbiota and to develop targeted approaches to manipulate microbiota interactions. To illustrate, bacteriophages, which are viruses that infect bacteria and archaea, have long been known to be able to influence microbial communities by acting as vectors of horizontal gene transfer (Jain et al. 1999). Their dynamic interactions have been suggested to play crucial roles in the early years of life when the immune system is developing (Lim et al. 2015). In line with those observations, Chitong Rao et al. recently demonstrated that the fungal species *Candida albicans* can inhibit multiple dominant genera of gut bacteria, including *Escherichia* and *Klebsiella*, and thus affect the dynamic assembly of the gut microbiota in preterm infants (Rao et al. 2021). Additionally, inter-kingdom interactions among these microorganisms and their interactions with the host immune system have been found to be important for the effectiveness of fecal microbiota transplantation (FMT) (Lam et al. 2022). To address this challenge, multi-kingdom abundance quantification and ecological modeling methods, as well as experimental validation, are necessary.

(7) **From bench to bedside**: The use of microbiome-based therapies, such as prebiotics (Bindels et al. 2015), probiotics (Suez et al. 2019), and FMT (Hanssen et al. 2021), has generated significant interest in recent years and expanded to the development of small molecule drugs targeting gut microbes or their interactions with hosts (Cully 2019). Moreover, a microbiota-directed complementary food prototype has shown promise for treating undernourished children (Chen et al. 2021). However, the efficacy and safety of those microbiome-based therapies require further and through study. A recent retrospective evaluation of FMT safety, which included 8547 Chinese patients over a nine-year period (Tian et al. 2022a), concluded that "FMT appears safe at both short-term and long-term follow-up". Hence, there is a need for further research to develop and improve microbiome-based therapies while also comprehending their underlying mechanisms of action. The ultimate goal is to design interventions that are more potent, which target not only the gut microbiota but also the entire gut ecosystem. This will allow for the treatment and more importantly the prevention of gut-related diseases.

(8) **From microbiome to phenome and precision medicine**: Personalized diagnosis, prevention, and treatment of human diseases require integration of all relevant clinical phenotypes, including the gut microbiome (Price et al. 2017). To this end, the Human Phenomics Project (HPP) was initiated (Tian et al. 2022b). Studies have shown that the gut microbiome can aid in the diagnosis of T2D development (Wu et al. 2020; Zhou et al. 2019) and in designing personalized nutrition to treat glucose spikes (Zeevi et al. 2015). Within the context of big-data-driven revolution of precision medicine, it is feasible to access and optimize the health trajectory of each individual (Yurkovich et al. 2019). However, it is crucial to determine the extent to which the gut microbiome contributes to the disease, compared to genetic and other environmental risk factors. This is necessary to establish the human gut microbiome as a unique opportunity and hope for personalized medicine, rather than a mere hype.

To tackle these obstacles, it is imperative to establish international collaborations and consortia. Such collaborations would bring together researchers from different fields and regions, fostering the convergence research model, which is the hallmark of the 'third revolution' in life sciences. Such collaborative effort is also critical for advancing our comprehension of the gut microbiome and for translating this knowledge into better health outcomes for patients. Step by step, piece by piece, we should be able to achieve the Yin-Yang balance between our gut microbes and us humans.

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