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REVIEW

Application of metagenomics in the human gut microbiome

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Abstract

There are more than 1000 microbial species living in the complex human intestine. The gut microbial community plays an important role in protecting the host against pathogenic microbes, modulating immunity, regulating metabolic processes, and is even regarded as an endocrine organ. However, traditional culture methods are very limited for identifying microbes. With the application of molecular biologic technology in the field of the intestinal microbiome, especially metagenomic sequencing of the next-generation sequencing technology, progress has been made in the study of the human intestinal microbiome. Metagenomics can be used to study intestinal microbiome diversity and dysbiosis, as well as its relationship to health and disease. Moreover, functional metagenomics can identify novel functional genes, microbial pathways, antibiotic resistance genes, functional dysbiosis of the intestinal microbiome, and determine interactions and co-evolution between microbiota and host, though there are still some limitations. Metatranscriptomics, metaproteomics and metabolomics represent enormous complements to the understanding of the human gut microbiome. This review aims to demonstrate that metagenomics can be a powerful tool in studying the human gut microbiome with encouraging prospects. The limitations of metagenomics to be overcome are also discussed. Metatranscriptomics, metaproteomics and metabolomics in relation to the study of the human gut microbiome are also briefly discussed.

Key words: Human gut microbiome; Metabolomics; Metagenomics; Metaproteomics; Metatranscriptomics

Core tip: Metagenomics plays a role in understanding the human gut microbiome, including the diversity of the gut microbiome, identifying novel genes, and determining the etiology of functional dysbiosis. A combination of metagenomics, metatranscriptomics, metaproteomics and metabolomics can also promote an understanding of the functional activity of the human gut microbiome and possibly provide a new strategy for disease diagnosis and treatment.

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INTRODUCTION

The human gastrointestinal tract harbors an extremely complex and dynamic microbial community, including archaea, bacteria, viruses and eukaryota[1]. Most of the microorganisms residing in the gastrointestinal tract are bacteria, with a density of approximately 10^{13}-10^{14} cells/g fecal matter, in which 70% of the total microbes colonize the colon[2]. The gut microbial community plays an important role in protecting the host against pathogenic microbes[3-5], modulating immunity[6,7], regulating metabolic processes[8,9], and is regarded as a neglected endocrine organ[10]. Recently, the role of the human gut microbiome has been well reviewed[11-13].

Classical studies of the gut microbiome have been largely dependent on cultivation techniques. However, traditional culture methods only cultivate 10%-30% of gut microbiota[14-16]. With the rapid development of advanced molecular technologies such as PCR-denaturing gradient gel electrophoresis, it has been shown that the gut microbial ecosystem is far more complex than previously thought[17]. In recent years, several next-generation sequencing technologies have been developed[18,19], which further facilitate the analysis of a large number of microorganisms in different environments[20-22] and human body sites[23], including the human gut[24-26]. 16S rDNA sequence analysis and metagenomics are two effective DNA sequencing approaches, and both have been used to study uncultivated gut microbial communities. The former focuses on the sequencing of the conserved 16S rDNA gene present in all microbes[27,28], and has established a series of novel connections between intestinal microbiota composition and disease[29-31]. The research based on 16S rDNA sequence attempts to reveal "who's there?" in a given microbial community, while shotgun metagenomic sequencing can be used to answer the complementary question of "what can they do?"[32,33].

Metagenomics was first described in 1998 by Handelsman and Rodon[34,35], and became another DNA sequencing approach to study the complex gut microbial community. It aims to catalog all the genes from a community by the random sequencing of all DNA extracted from the sample[36-38]. Firstly, the total DNA of all microorganisms is extracted from fecal samples. Before being sequenced, total DNA samples are randomly sheared by a "shotgun" approach. The comprehensive sequences are then analyzed to obtain either species profiles based on phylogenetic markers (16S rDNA)[39] or genomic profiles based on whole genomes[22]. The shotgun sequence reads are filtered to obtain the high-quality sequences for the whole genomic profile by metagenomics. Based on sequence overlaps, the filtered sequences are then assembled to form longer genomic sequence contigs. Computational methods are needed to code sequences in the contigs. Data mining and database searches applying different powerful algorithms are then used to annotate genes[40]. The information obtained from the sequence-based and functional metagenomics enables a more comprehensive understanding of the structure and function of microbial communities than ever before.

METAGENOMICS IN STUDYING THE HUMAN GUT MICROBIOME

Metagenomics: Revealing the diversity of the human gut microbiome

The European project, MetaHIT[37], and the American Human Microbiome Project[25,41] have contributed to the availability of the reference gene catalog. These projects have facilitated the study of the human intestinal microbiome using metagenomics. By applying metagenomics to investigate fecal samples from 124 European individuals, the MetaHIT consortium found 3.3 million non-redundant genes in the human gut microbiome for the first time. Surprisingly, the gene set was 150 times larger than the human gene complement. Moreover, over 99% of the genes in the human gut microbial communities were bacterial, which indicated that the entire cohort harbored more than 1000 bacterial species[37]. However, the number of genes in the human gut microbiome was expanded more than threefold by subsequent analyses[42,43]. These observations further completed the catalog of reference genes in the human gut microbiome.

A core human gut microbiome has also been explored[44]. The average human intestinal microbiome is now better defined and comprises approximately 160 bacterial species in each individual[37]. Moreover, on average, individual microbiota could have long-term stability[45,46]. By applying low-error 16S ribosomal RNA amplicon sequencing and whole-genome sequencing methods to characterize bacterial strain composition in the fecal microbiota of 37 patients in the United States, Jeremiah and colleagues[45] found that on average, their individual microbiota was remarkably stable and 60% of strains remained over the course of five years. From the in-depth profiling of metagenomic datasets derived from fecal metagenomes of healthy individuals, the human gut has been postulated to consist of three enterotypes, typified by the relative dominance of particular groups of organisms: *Prevotella*, *Ruminococcus* and *Bactericides* spp[47].

In addition, studies using different methods including metagenomics have found a series of factors that can influence the composition and diversity of the gut microbiome, such as diet[48-50], age[51,52], geography[51,53], drugs[54,55], and environmental substances[56]. For example, a study found that due to the difference in long-term dietary habits, human gut microbiome abundance and proportions varied between United States individuals. Furthermore, species composition, but not enterotype, in these subjects was affected by short-term changes in diet[57]. In the MARS-500 study, Mardanov *et al*[58] found dynamic changes in the gut microbiome in participants

using metagenomic analysis.

Functional metagenomics: Discovering novel genes and microbial pathways

In recent years, due to the rapidly developing computational methods critical for the analysis of metagenomic data and earlier surveys performed on marine and other environmental microbiome, more and more studies have focused on functional metagenomics of the human gut microbiome[37,38,51,59]. *Escherichia coli* (*E. coli*) is the most commonly used host for functional metagenomics, and genes from a large diversity of bacteria can be expressed within *E. coli*[33]. Furthermore, other species such as *Streptomyces*, *Bacillus subtilis* and *Lactococcus lactis* can also be used to promote the heterologous expression of Gram-positive bacterial DNA[60].

Hehemann and colleagues[61] found genes encoding the enzymes porphyranase and agarase from the gut microbiome in Japanese individuals, but not in North Americans. Interestingly, the marine Bacteroidetes are widely found in seaweed, and many Japanese eat seaweed regularly[61], thus it is likely that these functions were acquired from these organisms by lateral gene transfer.

The catabolism of dietary fibers is important for human health[32]. Carbohydrate active enzymes (CAZymes), produced by human intestinal microorganisms, can degrade components of dietary fiber into metabolizable monosaccharides and disaccharides. However, before metagenomics were used to study the human gut microbiome, the study of CAZymes was restricted to cultivated bacterial species. Several metagenomics studies focusing on the gut microbiome determined the diversity of CAZymes, revealing the human gut microbiome to be a surprisingly rich source of carbohydrate active enzymes[36,38,62,63]. In addition, Tasse *et al*[64] detected novel CAZymes using functional metagenomics on human gut microbial genes. The function-based screening of intestinal metagenome libraries also identified a large genetic repertoire of genes encoding bile-salt hydrolase enzymes[65]. These functions were selectively enriched in intestinal microorganisms. Furthermore, novel β-glucuronidase activity, dominant in healthy adults and children, from Firmicutes was revealed by the functional screening of large insert metagenomic libraries of *E. coli* clones independent of culturability[66].

Recently Vital and colleagues[67] performed an extensive analysis of butyrate-producing pathways and individual genes by screening thousands of sequenced bacterial genomes from the Integrated Microbial Genome database. They found that the genomes of 225 bacteria had the potential to produce butyrate, including many previously unknown candidates. Most candidates belonged to distinct families within Firmicutes[67]. These authors also used the established gene catalog to screen for butyrate synthesis pathways in 15 metagenomes obtained from the fecal samples of healthy individuals. The results revealed that a high percentage of total genomes exhibited a butyrate-producing pathway, and the most prevalent was the acetyl-coenzyme A pathway, followed by the lysine pathway[67].

Functional metagenomics: Investigating antibiotic-resistance genes

Many bacterial infections are becoming more and more difficult to treat, partly due to the increasing antibiotic resistance of human pathogens[68-70]. Recent studies have revealed that some human commensal microbiota harbor numerous antibiotic-resistance genes (ARGs), which have led to the human gut-associated resistome[71,72]. Thus, it is important to understand the contribution of the whole microbiota of particular systems to antibiotic resistance[73].

The first population-level analysis of resistance gene prevalence in the human gut was performed by Seville *et al*[74]. Interestingly, they found that several of the tested genes were common in human microbiomes using microarray probes to identify 14 tetracycline and macrolide-resistance genes in the fecal and saliva samples of 20 healthy volunteers from England, Finland, France, Italy, Norway, and Scotland. However, the fecal samples from France and Italy showed significantly higher levels of some tetracycline and erythromycin genes than those of the samples from Scandinavia or the United Kingdom.

Compared with previous methods, the metagenomic approach is a powerful tool that can help us to gain a more comprehensive understanding of the ARGs in human gut microbes. By analyzing the genomic content of a microorganism, it is possible to predict the resistance phenotype and adapt a specific treatment. Functional metagenomics can be used to isolate completely novel ARGs from the non-cultivable fraction of the microbiota and reveal the complex background context in which antibiotic resistance evolves in both microbial and host communities.

By employing fecal metagenomic data from different countries, studies have confirmed that resistance gene prevalence exists in the human gut microbiome and the distribution of ARGs are different between countries[75,76]. Moreover, Forslund *et al*[75] found associations between transposable elements in the tested genes, which is consistent with the finding that ARGs can be exchanged among gastrointestinal microbes[77], particularly during host stress[78].

Sommer *et al*[72] screened the gene inserts that caused resistance in *E. coli* to 13 different antibiotics by performing functional metagenomics screening of fecal and oral samples from two human donors. They then compared these genes with previous homologs in pathogens and found a considerable diversity of ARGs in the microbes. Cheng *et al*[79] first applied the strategy of screening a relatively large-insert fosmid library generated from the gut microbiota of four healthy candidates. The library was used to screen for ARGs against seven antibiotics. The authors identified a variety of previously unknown resistance determinants and found that only the N-terminus conferred kanamycin resistance following a functional

study on the new kanamycin resistance gene.

Recently, Moore *et al*[80] used functional metagenomics in fecal microbiota from 22 healthy infants and children to identify ARGs. They not only identified three novel resistance genes, but also reported their results on resistance to folate-synthesis inhibitors conferred by a predicted Nudix hydrolase, which was an important part of the folate-synthesis pathway. In addition, their functional metagenomic investigations demonstrated that fecal resistomes of healthy children had a higher diversity than previously suspected.

Metagenomics: Finding functional dysbiosis

As reported, dysbiosis of the intestinal microbial community is associated with some diseases, including inflammatory bowel disease[81-83], obesity[38,84-86], diabetes[87-89], allergy[90,91], irritable bowel syndrome (IBS)[92], colorectal cancer[93-96], liver cirrhosis[97-99], nonalcoholic steatohepatitis[100,101], neurodevelopmental disorders[102,103], cardiovascular disorders[104], cholesterol gallstones[105], diarrhea[106], malnutrition[107], kidney disease[108], and colon polyps[109]. Recently, in a metagenomic analysis of the stool microbiome in patients receiving allogeneic stem cell transplantation, Holler *et al*[110] found a relative shift from a predominance of commensal bacteria toward *Enterococci*, which was particularly marked in patients who subsequently developed or suffered from active gastrointestinal graft-*vs*-host disease.

In addition to identifying dysbiosis of the human gut microbiome in some diseases, metagenomics can determine novel changes in microbial functions. A study using the metagenomic approach in patients with type 2 diabetes performed by Qin *et al*[87] found a moderate variation in the microbial composition of the gut between cases and controls. Microbial functions conferring sulfate reduction and oxidative stress resistance were also more abundant in patients with type 2 diabetes than in healthy controls. Similarly, Wei *et al*[98] analyzed the fecal microbiota of 20 hepatitis B liver cirrhosis patients and 20 healthy controls using metagenomic methods, and found an obvious change in fecal microbiota between the two groups. Importantly, compared with the controls, functional diversity was significantly reduced in the fecal microbiota in the patients. In addition, the fecal microbiota in the patients showed abundant metabolism of glutathione, gluconeogenesis, branched-chain amino acids, nitrogen and lipids, but a decrease in the level of aromatic amino acids, bile acid and cell cycle related metabolism.

Metagenomics can also be used to determine the interactions between intestinal bacteria and the host. Intestinal bacteria play an integral role in human health. However, the possible mechanisms related to the interactions between intestinal bacteria and the host are not understood. Lakhdari *et al*[111] used high-throughput screening technology to investigate intestinal microbial pathways, and found that *E. coli* metagenomic clones could modulate intestinal mucosal proliferation by activating the nuclear factor-κB pathway in epithelial cells[112-114]. Recently, by applying functional metagenomics, Dobrijevic *et al*[115] found that secreted and surface-exposed proteins from Gram-positive bacteria in the human gut microbiota played a role in immune modulation.

Metagenomics is also helpful in screening plasmid-encoding elements, especially with the improvement of methods for purifying high-quality and high-yield plasmid DNA[116]. The plasmid harbors numerous mobile genetic elements. A profound understanding of the mobile genetic elements associated with the human gut microbiota is meaningful as they can reflect the co-evolution of host and microbe in the human gut[32].

Jones and Marchesi[117] isolated novel plasmids from the human gut microbiota and revealed that some crucial genes were enriched in the human gut compared with other systems using the culture independent transposon-aided capture system. Recently, based on metagenomic analysis, several studies indicated that the horizontal gene could transfer between phylogenetically distant bacterial groups[64,65,118]. However, the triggers that promote this gene exchange are not known. Smillie *et al*[119] showed that ecology could be the main driver of gene exchange.

LIMITATIONS IN APPLYING METAGENOMICS

From the above findings (Figure 1), metagenomics have been shown to be an incredibly powerful technology in studying the human gut microbiome. However, there are still some limitations in the use of metagenomics, as shown in Figure 2. Firstly, it is not possible to identify microbial expression. Secondly, as metagenomics require much higher sequence coverage than 16S rDNA sequence analysis[120], the costs and time involved in DNA sequencing projects for gut metagenomics are far greater than those of 16S rDNA sequence analysis. Thirdly, to obtain high coverage required for metagenomics, a sufficient quantity and high quality of DNA samples are essential. Although precautionary steps are performed, human contaminants are found in 50%-90% of sequences[24]. Different DNA extraction kits and laboratories also have an impact on the assessment of human gut microbiota[121]. Comparing data across studies that use different bacterial DNA extraction methods is difficult[122]. Fourthly, to perform a metagenomic study successfully, the quality of the underlying functional annotations of metagenomic sequence fragments is very important. However, a significant proportion of data cannot be assigned a function due to a lack of close matches in reference databases[37]. For viral data, this situation is particularly severe, as 80% or more of sequence reads lack known matches[123].

Millions of sequences in each sample are required for functional gene analysis of a complex microbial community. It is difficult to identify and improve the accuracy of information derived from the relatively short gene fragments generated by next-generation sequencing,

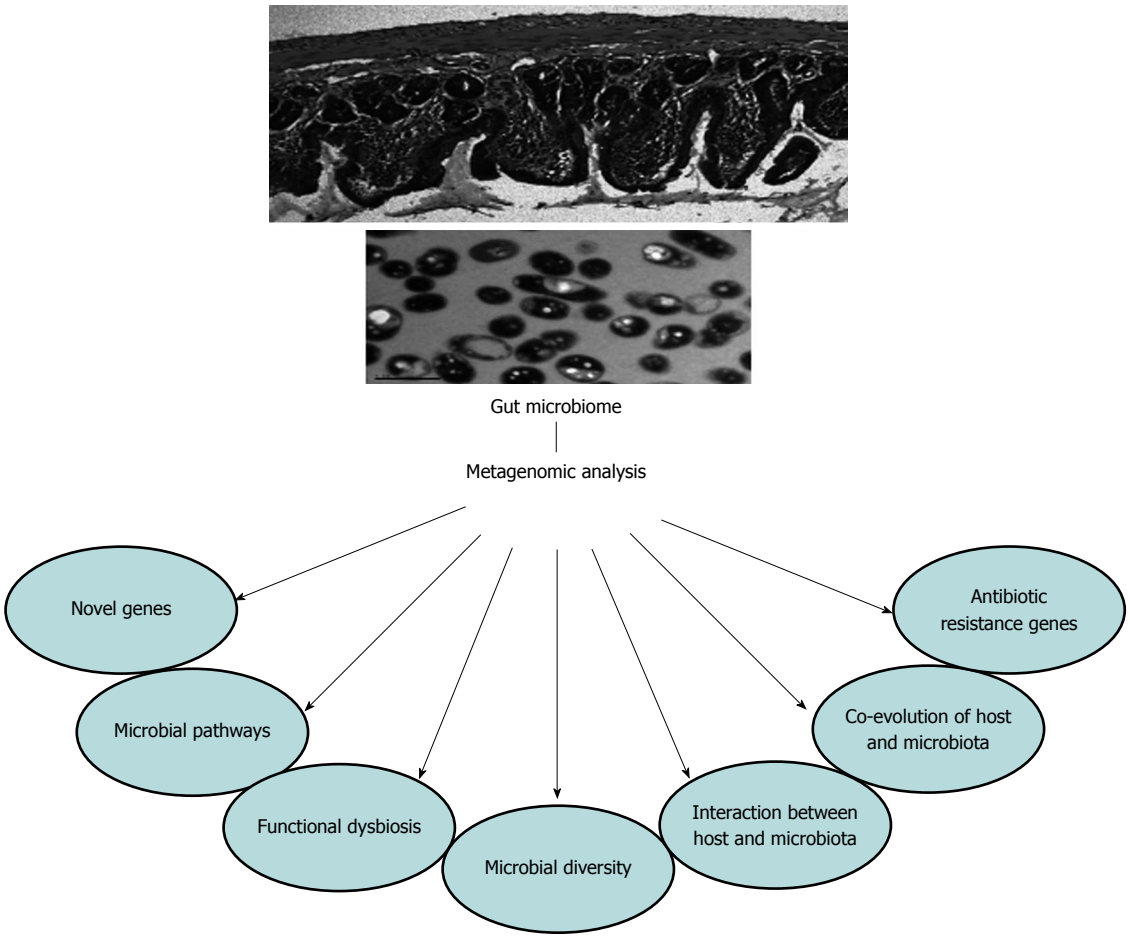

Figure 1 Application of metagenomics in the human gut microbiome. In studying the human gut microbiome, metagenomic analysis has the potential to provide sufficient information in the following research areas: The detection of microbial composition and diversity, novel genes, microbial pathways, functional dysbiosis, antibiotic resistance genes, and the determination of interactions and co-evolution between microbiota and host.

due to the many bioinformatics challenges proposed by the huge metagenomic shotgun sequencing. It is also difficult to assign function unambiguously based on sequence similarity alone, which may cause misannotation[124]. Moreover, when there are less abundant members of the microbiome or a community containing many closely related species, it may be difficult to assemble genomes[125]. This can lead to a situation where, even if a function can be ascertained, it may be a challenge to assign it to specific species within the microbial community. In addition, DNA is the material used in metagenomic sequencing, and the expression of each functional gene in a sample in a given environment is very difficult to determine.

METATRANSCRIPTOMICS, METAPROTEOMICS AND METABOLOMICS

Metagenomics is an extremely powerful tool that can be used to describe the genetic potential of the microorganisms present in a given environment. However, it has a very limited function in revealing their activity or gene expression. With the rapid development of metatranscriptomics[126], metaproteomics[127] and metabolomics[128], the functional activity of a microbial community can be identified.

Metatranscriptomic sequencing can be used to determine the activity of genes in a defined environment. Gosalbes *et al*[129] used metatranscriptomic analysis of fecal microbiomes from ten healthy humans, and found that carbohydrate metabolism, energy production and synthesis of cellular components were the main functional roles of the gut microbiota. In contrast, amino acid and lipid metabolism were reduced in the metatranscriptome.

Metatranscriptomics also has some limitations. Firstly, it is very difficult to obtain high-quality and sufficient amounts of RNA from environmental samples. Secondly, it is a challenge to separate the mRNA of interest from the more abundant types of RNA such as rRNA. Thirdly, the short half-life of mRNA leads to difficulty in the detection of rapid and short-term responses to environmental changes[130]. Fourthly, the reference databases are insufficient.

An analysis of proteins is also important to understand microbial functions. Recently, a study demonstrated that the fecal metaproteome in healthy adults was subject-specific and relatively stable over a one-year period[131]. In addition, some core functions, including carbohydrate metabolism

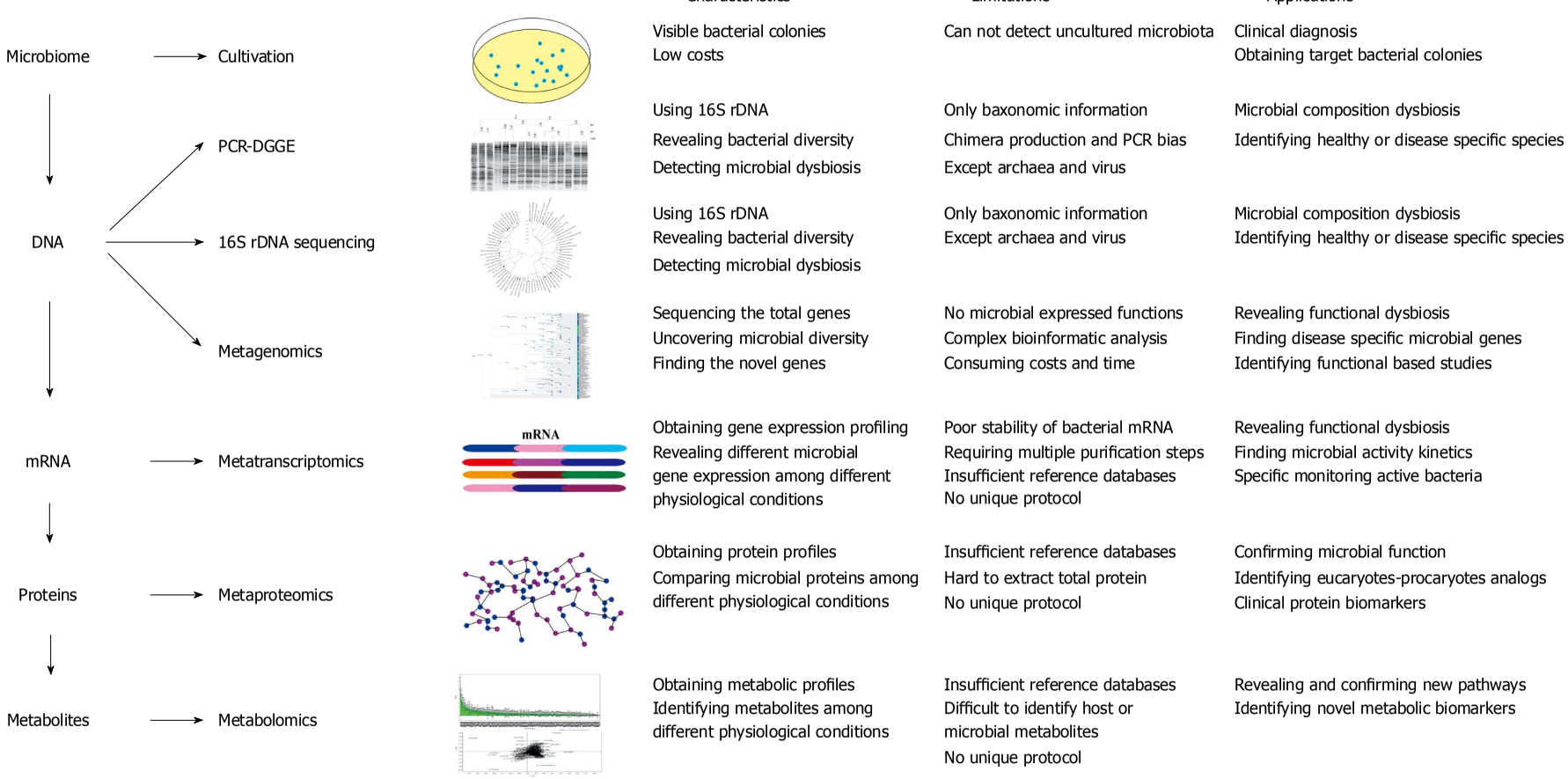

Figure 2 Comparison of different gut microbiome study approaches. The characteristics, limitations, and applications of different gut microbiome approaches from cultivation to metabolomics are presented. DGGE: Denaturing gradient gel electrophoresis.

and transport, were also determined. However, similar to metatranscriptomics, the ability to assign functional classifications is limited due to insufficient reference databases. It is a significant challenge to disentangle the complex array of proteins produced by the intestinal microbiota.

Currently, metabolomics is increasingly used to study the gut microbiome[132]. Some human intestinal disorders, such as colorectal cancer, inflammatory bowel disease and IBS, have been studied using metabolomics[133-136]. For instance, a study on patients with ulcerative colitis and IBS revealed that, compared with controls, the patients with ulcerative colitis had increased quantities of taurine and cadaverine. Importantly, a higher bile acid concentration and lower levels of branched-chain fatty acids were found in IBS patients[136]. Moreover, no significant changes were found in short-chain fatty acid and amino acid concentrations. However, some limitations restrict the development and clinical application of metabolomics. On the one hand, the metabolomics databases are incomplete and insufficient, and there are many metabolites that are not included

in the databases. On the other hand, the obtained metabolites are mixed, thus it is very difficult to identify the information from the host and the microbial metabolites.

As shown in Figure 2, though there are some limitations with these approaches, they have significant potential clinical applications. The combination of the meta-omics may be sufficiently powerful to elucidate the ecologic roles of the human gut microbiome[137].

CONCLUSION

In conclusion, metagenomics can not only identify the diversity of the human gut microbiome, but can also reveal new genes and microbial pathways, and uncover functional dysbiosis. The application of metagenomics has huge potential in revealing the mechanisms and correlations between the human intestinal microbiome and diseases. However, metagenomics also has limitations and requires improvement[138].

With the rapid development and application of metagenomics, as well as metatranscriptomics, metaproteomics and metabolomics, it is possible to identify new microbial diagnostic markers that will provide early diagnosis and novel treatments. Maximizing the contribution of microorganisms and identifying more probiotics are also very promising. Based on an increased understanding of the role of the human microbiome in diseases and their interactions, as well as inter-individual differences and physiologic parameters, the exploration of personalized medicine will progress immensely. In addition, it is possible to explore new antibiotics that target antibiotic resistance microbiomes based on a profound understanding of ARGs in the gut microbiome.

Current metagenomic studies of the human gut microbiome have been performed in limited cohorts, thus, it is necessary to enhance our understanding of the human gut microbiome by investigating human populations from different countries, for longer periods, and include multiple age groups[32], and various disease stages. A study of the characteristics of the human gut microbiome in different disease stages would help us understand the relationship between the gut microbiome and disease development, and thus would help to establish the optimal strategies for preventing, improving and even reversing diseases.

As metagenomics still has some limitations, it is necessary to combine other microbiome approaches, including cultivation methods, with a study of metagenomics in the intestinal microbiome. This will ensure that the results are more accurate and convincing. Recently, several studies have successfully used this combination and obtained meaningful findings[56,139-141]. To overcome the limitations of metagenomics, it is also important to create a unified microbial DNA extraction method, improve computational algorithms, and complete the reference databases.

The application of metagenomic technology in the human gut microbiome is in its infancy. However, it has been used in other environments, including soil and the sea, for some time. Thus, the success of applying metagenomic technology in studying these environments can be followed by further study in the human gut microbiome. In addition, the human gut harbors not only bacteria, but also eukaryota and viruses. To date, few studies on eukaryota and viruses using the metagenomics approach have been carried out, thus, the future study of the human gut microbiome using the metagenomics approach is promising and more efforts are urgently needed.

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