

EDITORIAL

## Gut microbiota: An emerging biological diagnostic and treatment approach for gastrointestinal diseases

Gut microbiota consists of trillions of microorganisms including bacteria, archaea, fungi, protists, and viruses. Different individuals have different compositions of gastrointestinal (GI) microbiota. The various microorganisms maintain a relatively stable ratio with each other, and are colonized in the lumen and mucosa of the digestive tract in a certain order to achieve a relatively stable microecological balance, and play physiological functions such as biological barriers to the host.<sup>1</sup> Gut microbiota dysbiosis can cause metabolic disorders, immune system activation, tumor responses to therapies, and so on. As the medical community has published and continues to generate microbiome data and integrate them with transcriptomics, proteomics, metabolomics, and clinic phenotypes, novel microbial biomarkers associated with diseases will be identified in many GI diseases. These microbial biomarkers have the potential value to be translated into biological approaches for diagnostics and treatments.

The oral cavity is the first part of the human digestive tract. The oral microbes can enter the downstream digestive tract through saliva or food and can also be detected in tissue distant from the oral cavity. Oral microbes are closely correlated with multisystemic diseases such as gastrointestinal cancer, type 2 diabetes, cardiovascular disease, and rheumatoid arthritis.<sup>2–6</sup> As to digestive tumors, oral microbiota has been suggested to play a potential role in the etiology of esophageal cancer, colorectal cancer (CRC), and pancreatic cancer.<sup>7–9</sup> It has been reported that the oral periopathogens *Fusobacterium nucleatum* and *Porphyromonas gingivalis* are essential in the development of colorectal and pancreatic cancer, respectively.<sup>10,11</sup> The use of oral microbiome as a biomarker is gaining momentum. We characterized the salivary microbiota in patients at different histological stages of gastric carcinogenesis and identified a distinct salivary microbiota in patients with gastric cancer when compared to those with superficial gastritis and atrophic gastritis. An enrichment of oral pro-inflammatory microorganisms including *Corynebacterium* and *Streptococcus* is likely an important factor contributing to the development and progression of gastric cancer. A random forest model was constructed based on the salivary microbiota profiles, and showed an excellent performance in distinguishing gastric cancer from patients with superficial gastritis and atrophic gastritis, yielding an area under the curve (AUC) of 0.91.<sup>12</sup> In addition, other studies also showed a high sensitivity rate (AUC of 97%) using oral microbiota to screen for gastric cancer including microbiota on tongue coatings.<sup>13,14</sup> However, the use of oral microbiota as biomarkers for gastric cancer requires further investigation and verification.

The stomach has a unique microenvironment with gastric acid and mucus. The gastric microbiome recently revealed dysbiosis in different mucosal lesions including gastric ulcer, polyps, and cancer.<sup>15–17</sup> The gastric microbial diversity and

richness in gastric tumorigenesis gradually reduces from gastritis, intestinal metaplasia, and intraepithelial neoplasia to gastric cancer.<sup>17–19</sup> Nevertheless, the available data on the gastric cancer microbiome are limited and specific microbiota as biomarkers for gastric tumorigenesis have not been established as yet.

The colon has the largest population of microbes in our body. Recent studies have revealed that microbiota dysbiosis has links with functional gastrointestinal disorders (FGIDs), inflammatory bowel disease (IBD), CRC, and other GI disorders. FGIDs are currently defined as a group of nonorganic GI diseases that lack biological markers for their diagnosis and treatment. Microbiota alterations may induce FGID symptoms through fermenting ingesta, modulating bile acid metabolism, changing intestinal immune function and motility, and visceral sensation. Microbiota alteration in the gastric fluid was reported in patients with functional dyspepsia,<sup>20</sup> and fecal microbiota dysbiosis was demonstrated in irritable bowel syndrome (IBS)<sup>21</sup> and functional constipation.<sup>22</sup> Evidence indicates that gut microbiota dysbiosis very likely contributes to some FGIDs, IBS, and functional constipation. However, thus far, the findings of gut microbiota in IBS and functional constipation have been inconsistent. Nevertheless, manipulation of microbiota remains a promising treatment for at least some FGIDs.

Based on the roles and alterations of intestinal microbiota in FGIDs, potential treatments for the dysbiosis of IBS and constipation include probiotics, prebiotics, synbiotics, antibiotics, and fecal microbiota transplantation (FMT). Preliminary studies already show some benefit.<sup>23,24</sup> In particular, FMT is now being studied in functional bowel diseases and may be a new option for constipation refractory to conventional therapies.<sup>22</sup> However, the results of FMT for the treatment of IBS are discrepant; current evidence from RCTs does not suggest a benefit of FMT for global IBS symptoms.<sup>25</sup> However, gut microbiota could still be a diagnostic biomarker or therapeutic objective in the management of FGIDs.

Studies have demonstrated that gut microbiota appear to contribute to the development of pancreatic cancer, IBD, and CRC. We found that fecal microbes and butyrate as potential biomarkers may help to distinguish patients with pancreatic ductal adenocarcinoma from patients with autoimmune pancreatitis and healthy subjects.<sup>26</sup> Some intestinal bacteria like *Streptococcus bovis*, *F. nucleatum*, *Bacteroides fragilis*, and *Escherichia coli* are associated with ulcerative colitis and CRC.<sup>27,28</sup> These and other fecal microbial biomarkers have been used to predict CRC with good diagnostic performance.<sup>29–31</sup> Apart from being diagnostic or prediction markers, gut microbiota may be used to predict responses to various therapies in colon and other cancers. Many studies have found a relationship between the gut

microbiota and the efficacy and toxicity of chemotherapies and immunotherapies. Gut microbiota plays an important role in the metabolism and function of pharmaceuticals, and it can modify the toxicity of most chemotherapeutic drugs through effects on drug absorption, breakdown, and toxicity as illustrated by drugs such as 5-fluorouracil, oxaliplatin, and irinotecan.<sup>32,33</sup> In recent years, immunotherapy has been introduced to treat patients with advanced CRC. Gut microbiota can be potentially harnessed to promote the antitumor immune response and immunotherapeutic drug efficacy in CRC by effects on T-cell activation. The CTLA-4 blocker and PD-1 blockers work in concert with specific gut microbiota to affect tumor growth.<sup>34</sup> The detection and use of gut microbiota such as FMT to treat GI cancer have potential benefits, and current findings are only the beginning.

The roles of gut microbiota in GI diseases have received more and more attention. Beyond basic medical research, clinical trials modulating gut microbiota like FMT have yielded many unexpected and informative results for treating *Costridium difficile* infection, IBD, and other GI disorders.<sup>35,36</sup> Researchers are joining forces with business to advance GI microbiota translational studies and are opening up new opportunities for the prevention, diagnosis, prediction, and treatment of GI diseases.

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