Mucosal surfaces that line our gastrointestinal tract are continuously exposed to trillions of bacteria that form a symbiotic relationship and impact host health and disease. It is only beginning to be understood that the cross-talk between the host and microbiome involve dynamic changes in commensal bacterial population, secretion, and absorption of metabolites between the host and microbiome. As emerging evidence implicates dysbiosis of gut microbiota in the pathology and progression of various diseases such as inflammatory bowel disease, obesity, and allergy, conventional treatments that either overlook the microbiome in the mechanism of action, or eliminate vast populations of microbes via wide-spectrum antibiotics need to be reconsidered. It is also becoming clear the microbiome can influence the body’s response to therapeutic treatments for cancers. As such, targeting the microbiome as treatment has garnered much recent attention and excitement from numerous research labs and biotechnology companies. Treatments range from fecal microbial transplantation to precision-guided molecular approaches. Here, we survey recent progress in the development of innovative therapeutics that target the microbiome to treat disease, and highlight key findings in the interplay between host microbes and therapy.

Keywords: microbiome, therapeutics, fecal transplantation, inflammatory bowel disease

Introduction

The gastrointestinal (GI) microbiome is a diverse community of bacteria, archaea, fungi, protozoa, and viruses that have colonized the surfaces of the GI tract of all mammals. Since the closure of the Human Microbiome Project funded by National Institutes of Health (NIH) in 2012, our understanding of the functional characteristics and composition of gut microbiota have advanced. More than 10^{13} microorganisms in the intestine with approximately 1,000 species have critical physiological roles (Neish, 2009), and their microbial compositions differ along the digestion and diet of the host (Aron-Wisnewsky and Clement, 2016). It is estimated that genes from commensal microbiome outnumber at least 100-fold more than the human somatic genome (Belkaid and Naik, 2013). Six bacterial phyla of Firmicutes, Proteobacteria, Bacteroidetes, Fusobacteria, Actinobacteria, and Verrucomicrobia dominate the gut microbiota of healthy adult subjects. Among them, Bacteroidetes and Firmicutes phyla occupy up to 70–90% of total bacteria in the healthy adult GI tract followed by Actinobacteria, Proteobacteria, and Verrucomicrobia (Donaldson et al., 2016). Due to the complexity of the microbiome, it is difficult to determine the precise metabolic functions and cross-talk between the host and microbiome or between the individual species. However, recent advances in DNA sequencing technology and computational biology have revolutionized the field of microbiomics.

It is well-understood that the gut microbiota and its metabolites play pivotal roles in host homeostasis, such as providing essential nutrients (Flint et al., 2012; LeBlanc et al., 2013), metabolizing indigestible dietary compounds such as dietary fiber into short-chain fatty acids (SCFA) (Duncan et al., 2003) and contributing to intestinal epithelial barrier and enhancing innate and adaptive immunity of the host (Round and Mazmanian, 2009).

However, this community that helps to protect our bodies from infection and maintain gut homeostasis can also become our enemy. Disruption of a balanced composition of gut microbiome is known to cause immunological dysregulation with diseases including inflammatory bowel disease (IBD), asthma, obesity, metabolic syndrome, or cancer models (DeGruttola et al., 2016). Altered gut microbiome affects microbiota-derived products and metabolites, including pro- and anti-inflammatory materials (Lopez et al., 2014). And some probiotics, such as Bifidobacteria and Lactobacillus, may re-establish the composition of the gut microbiome, leading to amelioration or prevention of gut inflammation and other intestinal or systemic diseases (Hemarajata and Versalovic, 2013).

With the wealth of emerging research that implicates the microbiome in health and disease, the development of ther-
Fecal Microbiota Transplantation (FMT) in Clostridium difficile infection (CDI)

FMT for gut diseases has been well-studied for CDI (Bagdassarian et al., 2015; Kelly et al., 2015; Vindigni and Surawicz, 2017; Khanna, 2018), and has also been applied to antibiotic-resistant gastrointestinal infections (Vindigni and Surawicz, 2017). The stool of recurrent CDI patients have low microbial diversity and numbers after being exposed to several episodes of antibiotics. Since a first report of successful enema-based FMT treatment for CDI in 1983 (Schwan et al., 1983), various techniques for FMT have been evolved to treat CDI successfully. Compared to probiotic treatments that contain a few bacterial species, FMT involves thousands bacterial species native to the GI. FMT increases microbial diversity, restoring gut microbiota community structure and diversity to the level of a healthy person with a few exceptions of adverse effect in some cases. Therefore, there is intensive interest in FMT for CDI using capsule-based and enema-based therapies (Andremont, 2017). The closest microbe-derived enema-based drug to the clinic for CDI is RBX2660 developed by Rebiotix Inc in Minnesota, USA (Dubberke et al., 2016). RBX2660 is microbial suspension derived from donor stool samples and specially formulated for therapeutic delivery. The drug is currently in Phase 3 (PUNCH CD 3) Trials, and had shown positive results in Phase 2 with clearance of vancomycin-resistant enterococcus. FMT for CDI has been extensively reviewed in (Khanna and Raffals, 2017; Khanna, 2018) and (Nishida et al., 2017).

FMT in IBD

Patients with IBD have differences in their gastrointestinal microbiome compared with healthy individuals, although it is unclear whether this is a cause or consequence of chronic inflammation. IBD is accompanied with decreased microbial diversity, for example with Bacteroidetes and Firmicutes, and also a decrease in SCFA-producing bacteria (Clostridium clusters, and Faecalibacterium prausnitzii). In addition, there is an increase in mucolytic, sulfate-reducing and pathogenic bacteria (Ruminococcus and Desulfovibrio) and invasive Escherichia coli (E. coli) (Nishida et al., 2017). However, IBD poses a more difficult problem in the application of FMT compared to CDI. As such, the modulation of the microbial population in IBD with healthy whole stool would seem a viable treatment course.

Although early studies using FMT to treat IBD were very promising, with significant remission reported over long-term follow-up (Bennet and Brinkman, 1989; Borody et al., 2003), consensus on recent studies have been less encouraging. The differing outcomes are potentially linked to significant variations in sample size, treatment approaches and study designs (Kelly et al., 2015). Remission rates of 36.2% were reported when using meta-analysis of 18 studies, but were highest in young patients at 64.1% and those with Crohn’s Disease (CD) among IBD patients at 60.5%. However Ulcerative Colitis (UC) patients among IBD patients had a remission rate of 22% (Colman and Rubin, 2014; Suskind et al., 2015).

Three recent double-blind randomized control trials have been published for UC (none for CD) (Moayyedi et al., 2015; Rossen et al., 2015; Browne and Kelly, 2017; Paramsothy et al., 2017). In a study by Moayyedi et al. (2015) 75 participants received either stool from 6 healthy donors, or placebo, once per week for 6 weeks. The trial was stopped early due to futility with low likelihood of reaching clinical endpoint. Here, the patients did not receive bowel lavage before FMT and none achieved clinical remission. Interestingly, further genomic analysis revealed a dependence on donor material versus outcome, wherein one donor induced 39% remission in patients versus other donors at 10%. This link between donor microbial consortia and treatment outcome is indicative that complexities exist with whole stool samples therapies that require careful consideration. In a study by Rossen and colleagues (2015), the treatment course differed as FMT was administered twice, timed two weeks apart, and via nasal-duodenal infusion. Stool was collected from 15 healthy donors, and patients were, in this case, subject to bowel lavage before FMT. This study was also halted early due to futility, however, in the end, 30.4% of the patients in the treatment group achieved remission, compared to 32.0% of the patients in the placebo group. A third trial by Paramsothy and coworkers reached completion (Paramsothy et al., 2017). Patients were treated 5 days per week for 8 weeks. Here, patients received bowel lavage as in the Rossen study. Unique to this study though was the pooling of stool samples from 3–7 patients prior to administering FMT by colonoscopy and enema. 32% in the treated group achieved remission versus 10% in the placebo group. Since the treatment stool was pooled, success of the study could not be correlated to one donor.

It is clear from these studies that FMT treatment outcomes for IBD are complicated by numerous factors, such as differences in treatment regimens, stool preparation/formulation, and dosing frequencies. This is likely compounded by potentially varied levels of microbial dysbiosis within patients, and differing compositions of microbes from donors and recipient patients. In addition, these studies experienced a small number of patients with serious adverse effects from treatment, including worsening colitis, abdominal pain, and clinical deterioration (Browne and Kelly, 2017). There are limited available data on the safety profile for FMT in IBD, however, in general, side effects are less severe compared to the normal disease progression. In any case, this has not prevented further clinical testing. At the time of writing this review, there were 27 ongoing clinical trials using FMT to target IBD either active, or recruiting volunteers. Notably, two new clinical trials are underway at Boston Children’s Hospital.