In Translation

Improving ICI outcomes with a little help from my microbial friends

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Gut microbiome composition correlates with responsiveness to immune checkpoint inhibitor therapy. In a recent study in Science, Baruch et al. manipulated gut microbiome composition in patients with refractory metastatic melanoma using fecal microbiota transplants. Fecal microbiota transplant was safe and partially effective in inducing remission in refractory patients.

Immune checkpoint inhibitors (ICIs), including those that target programmed cell death protein 1 (PD-1) and related pathways, have drastically improved outcomes for many cancers. However, current anti-PD-1 therapies have limitations, including wide ranges in effectiveness across patient populations and immune-related adverse events (irAEs). Therefore, a key translational goal is to elucidate the mechanisms of ICI-refractory cancer and identify biomarkers to predict and manipulate ICI responses to enhance efficacy and limit side effects.

The gut microbiome has recently gained attention as a potential predictor and modifiable variable for ICI treatment response (Gopalakrishnan et al., 2018; Matson et al., 2018; Routy et al., 2018). An individual’s gut microbiome is the collection of bacteria, fungi, archaea, and viruses that resides in their gastrointestinal tract. The microbiome is essential for immune development and regulation, processing of complex carbohydrates, and exclusion of potential pathogens. Recent studies have identified microbial and immunological features that correlate with response to ICI therapy (Gopalakrishnan et al., 2018; Matson et al., 2018; Routy et al., 2018). These features include a variety of microbial taxa increased in abundance in responders (e.g., Ruminococcaceae, Enterococcaceae, Bifidobacteriaceae, and Akkermansia), cytokines associated with anticanccer immunity (e.g., IFN-γ and IL-12), and cytotoxic CD8+ T cells (Gopalakrishnan et al., 2018; Matson et al., 2018; Routy et al., 2018). However, to date, no universal or consistent microbial taxa have been shown to predict or modulate response to ICI therapy in animal models and clinical practice.

Given the complexity of the gut microbiome and the various taxa implicated in ICI response, it seems unlikely that any single microbe can serve as a silver bullet against cancer-mediated immunosuppression. Microbes do not exist in a vacuum, instead living and functioning together in a delicately balanced community at the host interface. Therefore, an intriguing tool that could be used to direct the gut microbiome toward anti-PD-1 responsiveness is fecal microbiota transplant (FMT), which orally and/or rectally transfers a fecal sample from a donor with a desired phenotype into a recipient to restructure their gut microbiome. In a recent study published in Science, Baruch et al. conducted a clinical trial to test whether FMT could safely and effectively improve ICI response in patients with anti-PD-1-refractory metastatic melanoma, using FMTs from anti-PD-1 responders (Baruch et al., 2020; Figure 1A).

Baruch et al. enrolled ten anti-PD-1-refractory patients to receive FMT from two donors who achieved complete response with prior anti-PD-1 therapy. Participants were orally administered vancomycin, neomycin, and polyethylene glycol (PEG) bowel preparation solution to deplete their native microbiome (Figure 1A). Following microbiome depletion, patients received an FMT from one of two responsive donors via colonoscopy. Participants were then given orally administered FMT capsules every 14 days to maintain the transplanted microbiome, followed by nivolumab infusions 2 days later for a total of six cycles. Outcomes related to the immune response, microbiome, and disease progression were measured at regular intervals (Baruch et al., 2020; Figure 1A).

Of the ten study participants, three exhibited decreased tumor size after anti-PD-1 therapy following FMT. To assess the effects of the FMT on the host microbiome, Baruch et al. used 16S rRNA gene sequencing and metagenomic shotgun sequencing of stool to characterize the gut microbiome of the recipients throughout the study. Principal component analysis of 16S rRNA gene sequencing showed strong similarity between the gut microbiota of participants and their respective donor following transplantation, indicating that the FMT successfully altered the recipients’ microbiota to resemble their donor. An analysis of composition of microbiomes (ANCOM) test based on metagenomic sequencing data of donors and post-FMT recipients identified discriminatory bacterial taxa associated with each donor group, as well as enrichments of taxa that were previously identified as favorable toward immunotherapy (Gopalakrishnan et al., 2018; Matson et al., 2018; Routy et al., 2018). Finally, functional annotation of microbial genes using the MetaCyc database showed distinct metabolic profiles of the post-transplant recipients in a
donor-dependent manner. Unfortunately, none of these microbiome analysis tools revealed features that clearly differentiated patients who showed improved anti-PD-1 response following FMT from those who remained refractory (Baruch et al., 2020).

Interestingly, all three participants who responded to anti-PD-1 therapy received FMT from the same donor (donor 1). All five participants in this donor group had upregulated expression of genes associated with antigen presentation and innate immunity, including IL-12, which has shown potential as an immunotherapy (Nguyen et al., 2020; Routy et al., 2018). Intriguingly, all ten participants demonstrated statistically significant increased T cell activation but did not exhibit significantly increased T cell infiltration of the lamina propria or upregulation of genes related to T cell immunity within the tumor (Baruch et al., 2020). This suggests that increased responsiveness to anti-PD-1 therapy may not be exclusively responsible for improved tumor regression and that other pathways and processes may be contributing to increases in antitumor activity in these participants.

Non-specific host responses were also observed in the tumors of all participants regardless of donor group or outcome, which could be generally attributed to the combination of antibiotics, bowel preparation, and FMT without respect to microbial content. This included upregulation of genes related to anticancer immunity pathways, such as IFN-γ signaling, T cell activation, and antigen presentation. Two of the three participants who responded to anti-PD-1 therapy had increased CD8+ T cell infiltration of their tumors; however, this was not unique to responders, as three participants who lacked an objective response also had increased infiltration (Baruch et al., 2020). This further supports the possibility of improved antitumor activity through pathways independent of PD-1 signaling.

This study provides preliminary but exciting clinical evidence that a patient’s microbiome-host interface can be manipulated to improve response to ICI therapies. Importantly, FMTs have an excellent safety profile, though antibiotic-resistant bloodstream infections after FMT have been reported in immunocompromised individuals (DeFilipp et al., 2019). In the present study, the authors reported no adverse events other than a single case of mild bloating. Perhaps even more remarkable is the fact that although half of the participants developed severe immune-related adverse effects (irAEs) during their initial anti-PD-1 therapy, none of them experienced severe irAEs during their post-FMT anti-PD-1 regimen (Baruch et al., 2020). In support of FMT as a
modulator of ICI toxicity, a small case series of two patients demonstrated its utility in resolving steroid-refractory ICI-associated colitis (Wang et al., 2019). Taken together, modulation of the patient’s microbiota could impact not only ICI efficacy but also toxicity. FMTs therefore represent a relatively low-cost, low-risk, and minimally invasive strategy to enhance responsiveness to anti-PD-1 therapy, immune toxicity, and other ICI treatments.

Although this study carries significant impact demonstrating a new avenue to improve response to ICI therapy, there are limitations. Without the inclusion of a placebo group, it is impossible to quantify the confounding effects of the microbiota depletion (i.e., oral antibiotics and bowel preparation) or transplantation procedure (i.e., colonoscopy) on anti-PD-1 therapy. These factors alone are sufficient to alter microbiota community structure (Kwak et al., 2020) and could impact response to ICI therapy regardless of the microbial makeup of the donor FMT. Without elucidation of a mechanism underlying the increase in anti-PD-1 responsiveness, our ability to develop a safe and reliable therapy for clinical application is limited. The variable donor-dependent responses seen here also illustrate the importance of appropriate donor selection.

FMTs have many caveats and limitations to consider prior to broad implementation. They can be highly variable in efficacy and permanence, which can change depending on individual microbial taxa and patient physiology (Wilson et al., 2019). FMTs entail the transfer of a network of bacteria, which may depend on keystone species to confer a therapeutic benefit. If even a small number of critical species drop out, the microbiome structure may appear similar between donor and recipient by diversity metrics, but the beneficial phenotype may be lost (Wilson et al., 2019). Furthermore, FMTs should be screened for mult drug-resistant organisms to avoid inadvertent colonization or bloodstream infection by antibiotic-resistant pathogens (DeFilipp et al., 2019).

Reductionist approaches should be used to elucidate the mechanism(s) underlying immune modulation. Microbes in the donor FMT may influence the immune response through direct interaction with immune cells, production of immunomodulatory metabolites, exclusion of immunosuppressive commensals, or a combination of these and other mechanisms (Figure 1B). Once the underlying mechanism is characterized, more precise and reliable interventions can be developed and implemented to maximize a patient’s chance for an optimal response to the immunotherapy of choice (Figure 1C). Prior to beginning treatment, screening of a patient’s stool could serve as a predictive tool to identify which drugs the patient may respond best to and which host factors may limit response to therapy. For example, beneficial metabolites could be supplemented via engineered probiotics, optimized diet, or purified encapsulation. A detrimental taxon that is excluded by the microbiota of ICI-responsive patients could be eradicated from the commensal gut microbiota of patients with unfavorable predictive markers using targeted antibiotics or phage therapies. These targeted strategies could be supplemented by specialized diets and/or tailored FMTs to maximize their effect (Figure 1C). This study provides the first of many steps toward making this personalized medicine approach a reality.

REFERENCES


