Probiotic Gut Bacteria Enhance Cancer Immunotherapy in a Mouse Model of Melanoma


The exciting fields of cancer immunotherapy and the gut microbiome converge in a recent study from Sivan et al (Science 2015;350:1084–1089), in which the investigators elegantly illustrate the beneficial effects of gut Bifidobacteria in a mouse model of melanoma. The investigators suggest that the gut microbiota may be as critical to tumor suppression as therapy with the immune checkpoint inhibitor anti–PD-L1. Moreover, when administration of Bifidobacteria was combined in the immunotherapy in mice implanted with melanoma, tumor growth was essentially arrested.

The described discovery sequence mirrors what others have previously reported in colitis models. The investigators first noted that mice of the same strain (C57BL/6) exhibited differential melanoma growth rates and tumor-specific immune cell infiltrate based on the mouse vendor. Tumors grew more aggressively in mice from Taconic Biosciences (TAC) than in mice from Jackson Labs (JAX). These differences normalized when TAC mice were either transplanted with fecal microbiota from JAX mice or cohoused with JAX mice (leveraging coprophagic behavior of mice with consequent transfer of gut microbes), thus illustrating that specific gut microbiota could prevent tumor growth. Next, the investigators tested the possibility that manipulation of gut microbiota could treat tumors by first implanting tumor and then manipulating the gut microbiota. To do so, they examined the effects of JAX fecal microbiota transplantation alone or in combination with anti–PD-L1 therapy in TAC mice. Both strategies were effective alone, and synergistic when combined.

To identify the bacterial mediators of this protective/therapeutic effect, the investigators availed 16S ribosomal RNA sequencing and thereby identified Bifidobacteria as the genus-level taxon associated with antitumor T-cell responses. Further analyses narrowed the important bifidobacterial species to B breve, B longum, and B adolescentis. Noting that the first 2 of these bacterial species are common components of over-the-counter probiotic supplements, the investigators then demonstrated that a commercial cocktail of this supplement recapitulated the effects they observed with the fecal transplant. Finally, the investigators demonstrated that live Bifidobacteria are required and act indirectly through stimulation of host antitumor T-cell responses. Supporting this, neither heat-killed Bifidobacteria nor live Lactobacillus supplementation could recapitulate the observed effects, and Bifidobacteria were ineffective in CD8 T-cell-depleted mice. The investigators found no evidence for translocation of Bifidobacteria into mesenteric lymph nodes, spleen, or tumor.

Comment. Although melanoma research may not typically pique the interest of gastroenterologists or GI researchers, we should take note of this exciting study. Cancer, a multifaceted condition that spans all organ systems and persists as a global epidemic, represents a nascent application for microbiota-related research. As a community, we have already established important links between the gut microbiota, physiology, and a list of diseases that now includes skin cancer.

Metastatic melanoma is the model example for cancer immunotherapy success. Beginning with the introduction of ipilimumab (an anti–CTLA-4 antibody) and now with the addition of PD-L1 inhibitors, significant gains have been seen for the first time in controlling disease progression. Even these therapies offer room for improvement with progression-free survival remaining at <1 year (N Engl J Med 2015;373:23–34). The gut microbiota is a potentially modifiable factor influencing tumor immunity that may enable even greater efficacy, or even perhaps a better chance of preventing cancer altogether.

Bifidobacteria are identified by these investigators as commensal microbes that enhance antitumor immunity. As discussed, Bifidobacteria are presently sold as over-the-counter, first-generation probiotic supplements (Clin Gastroenterol Hepatol 2012;10:960–968). The molecular mechanism(s) by which these bacteria impact dendritic cells is not delineated in this study, but elucidating this may unlock further opportunities for targeted therapeutics.
the key feature a metabolic bacterial trait? If so, such knowledge may permit the design of next-generation probiotics. To clarify the pertinent host–microbe interactions, an investigation of additional gut microbiota is warranted: given the diversity of gut microbes, one might expect other bacterial players to bear similar effects. Finally, if gut bacteria can enhance antitumor immunity, it stands to reason that certain commensal microbes may specifically antagonize antitumor immunity as well. The ability to identify such bacterial taxa may improve our understanding of variability in the natural history of disease, permit more accurate prognostication, and potentially enable a microbiota-based therapeutic intervention.

As is reported in the same issue of Science, PD-L1 is not the only checkpoint inhibitor therapy that can be influenced by gut microbiota. Vetizou and colleagues concurrently report that the antitumor effects of CTLA-4 blockade depend on distinct Bacteroides species (Science 2015;350:1079–1084). These 2 important studies add additional complexity to understanding how gut microbes may influence a variety of cancer therapies. Additionally, it was reported previously that gut microbiota could modulate the anticancer immune effects of cyclophosphamide (Science 2013;342:971–976). This study differed from the more recent studies in that the postulated mechanism of action involved translocation of bacteria into secondary lymphoid organs with consequent priming of the antitumor immune response: a breach of small intestinal microbial barrier function induced by cyclophosphamide set up this cascade of events. In that study, Lactobacillus species were implicated as key bacterial mediators.

Several major challenges must be overcome before applying these findings to clinical practice. First, the human gut microbiota is tremendously diverse, much more so than the 2 microbiota studied here. Variability and dynamics of human Bifidobacterial representation, as well as of microbiota community structure and function, must be studied and understood in this context. Many standard concomitant therapies including antibiotics have poorly understood effects in altering antitumor immunity. The effect of diet, a major factor shaping the gut microbiota (Science 2011;333:101–104), is not described in this study. However, as we have recently shown, even a single diet ingredient can influence host–microbe interactions with significant physiologic consequences (Cell 2015;163:95–107).

Clinical trials proposing to incorporate the addition of live probiotic bacteria to cancer therapy may have to overcome several barriers. Several cytotoxic and immune checkpoint inhibitor chemotherapies, as well as radiation therapy, affect GI barrier function. Although many currently used probiotics appear relatively safe even in the setting of cancer therapy, infectious complications could occur. In our experience, the US Food and Drug Administration has required a strong burden of proof of the safety of probiotics in the cancer population and will likely continue to do so (Curr Opin Support Palliat Care 2015;9:157–162). These potential risks and the anticipated regulatory burden provide further motivation for investigators to identify clearly the molecular mechanisms by which Bifidobacteria influence the tumor. This knowledge will help to determine whether or not specific probiotic-derived molecules might be combined with cancer therapy in a purified form.

Altogether, the data presented in this study represent an exciting step in applying microbiota-based therapies toward shaping cancer therapy. In gastroenterology, we seek efficacious therapies for metastatic cancers of the pancreas, liver, and colon. Given the observations of Sivan et al, the gut microbiota may provide the missing link.