

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

Section Editor: Mark J. Ratain, MD

Manipulating the Microbiome to Improve the Efficacy of Immunotherapy



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H&O What is known about the role of the gut microbiome in cancer?

TG Research into the intersection between the commensal microbiota and cancer is just in its infancy. What is becoming clear is that the composition of gut commensals can profoundly impact the systemic immune response, both quantitatively and qualitatively. The most advanced data in this regard are connected to the host immune response against tumors and the efficacy of cancer immunotherapies.

H&O Why do some cancer patients have a strong immune response against a tumor?

TG This is a major question in the field that is being investigated using multiple genomics platforms in cancer patients. We know that part of the reason that some cancer patients have a strong immune response against a tumor is because of differences in the oncogene pathways that are mutated or activated in different cases. However, there are also data suggesting that germline genetic differences could make a contribution, as might environmental factors, such as the microbiota. It is likely that all of these dimensions intersect to dictate the magnitude of the endogenous immune response against cancer.

H&O Does the gut microbiome differ in patients with cancer vs those without cancer?

TG This is an interesting question that is just beginning to be investigated. There are some older data in the literature suggesting that species of *Bifidobacterium* can be decreased

in patients with colon cancer vs those with benign intestinal diseases, but more work needs to be done in this area.

H&O Could you describe your research into the role of the gut microbiome in cancer?

TG Our latest study was published in the November 2015 issue of *Science*. We used 16S ribosomal RNA sequencing from stool samples to identify one of the key commensal bacteria that support improved antitumor immunity in mice. We found that the only significant association was for *Bifidobacterium*, which showed a positive correlation with antitumor T-cell responses. Different cohorts of mice showed either high or low immune responses against their tumor, and these responses were completely mediated by the microbiota. Transferring fecal material from mice with “good” microbiota to mice with “bad” microbiota appeared to restore immune responses. This maneuver also improved response to treatment with anti-programmed death ligand 1 (PD-L1) antibodies. We found that the transferable component could be accounted for by strains of *Bifidobacterium*, and that consequently we could use administration of *Bifidobacterium* as a “drug” to improve efficacy of anti-PD-L1 therapy (Figures 1 and 2).

H&O Why is T-cell infiltration of solid tumors associated with favorable patient outcomes?

TG The collective data suggest that anti-programmed death (PD)/PD-L1 antibody therapy (and likely other immunotherapies) preferentially work by restoring the function of T cells already in the tumor microenvironment. So patients who

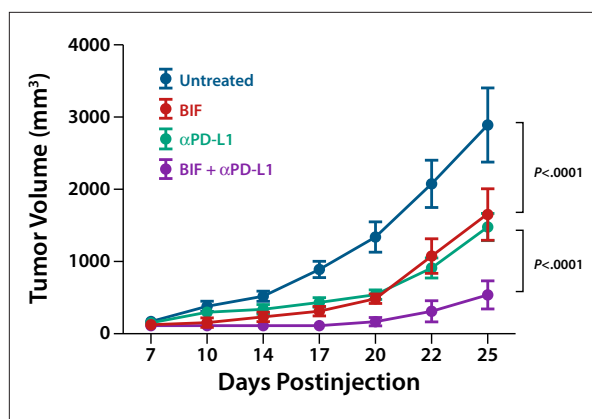


Figure 1. In a mouse model, administration of BIF improved efficacy of anti-PD-L1 therapy. BIF, *Bifidobacterium*; αPD-L1, antibodies targeting programmed death ligand 1. Adapted from Sivan A, Corrales L, Hubert N, et al. Commensal *Bifidobacterium* promotes antitumor immunity and facilitates anti-PD-L1 efficacy. *Science*. 2015;350(6264):1084-1089. Reprinted with permission from AAAS.

start off at baseline with a more potent endogenous immune response against their tumor are more likely to respond to immunotherapies. Our mouse data suggest that certain gut microbes can improve that endogenous immune response, which translates into improved immunotherapy efficacy.

H&O How might gut microbes stimulate the immune system to act against tumors?

TG Our own data suggest that certain gut microbes lead to a partial preactivation of the antigen-presenting cells of the body (ie, dendritic cells), which in turn makes induction of T-cell responses against tumors more likely to occur. Similar studies in virus infection models have found the same thing: that gut bacteria can help the systemic immune response.

H&O Is there a theory as to why the *Bifidobacterium* species in particular were linked to an antitumor immune response?

TG As mentioned above, it appears that the presence of *Bifidobacterium* in the gut can result in a low level of preactivation of dendritic cells in the mice, which translates into an improved spontaneous antitumor T-cell response and improved efficacy of checkpoint blockade immunotherapy. What we do not yet know in detail is the mechanisms by which gut bacteria can shape the biology of dendritic cells throughout the host. This question is the subject of current investigation.

H&O What are the potential implications of your study's findings?

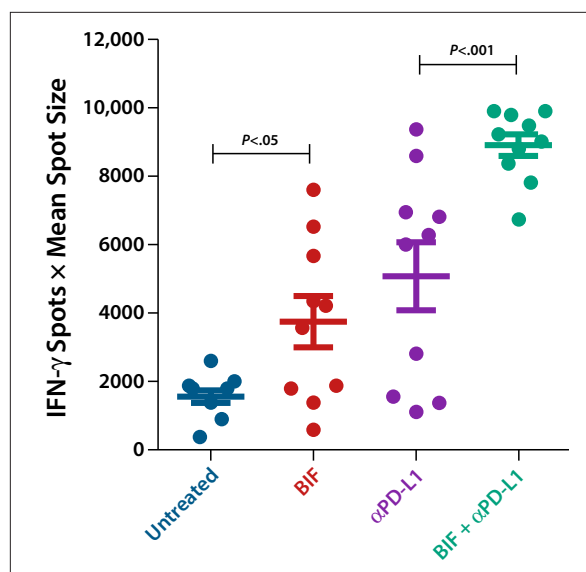


Figure 2. Induction of tumor-specific T cells in the periphery was increased with administration of BIF. BIF, *Bifidobacterium*; IFN, interferon; αPD-L1, antibodies targeting programmed death ligand 1. Adapted from Sivan A, Corrales L, Hubert N, et al. Commensal *Bifidobacterium* promotes antitumor immunity and facilitates anti-PD-L1 efficacy. *Science*. 2015;350(6264):1084-1089. Reprinted with permission from AAAS.

TG First, we need to know more about the human microbiota as it relates to cancer development, antitumor immune responses, and clinical efficacy of immunotherapies and other cancer treatments. Second, there is an opportunity to consider development of probiotics to “restore” a healthy microbiota and improve immune-mediated tumor control in patients. In principle, this approach could improve upon the efficacy of immunotherapy, just as we have seen in mouse studies.

H&O How could the microbiome be manipulated to improve the efficacy of immunotherapy?

TG If we can identify the key bacteria in humans that have similar effects as in the mouse studies, then we could perhaps integrate probiotics into cancer therapy. In humans, these bacteria may be *Bifidobacteria*, but they could also be other specific species. Therefore, the translational analysis of human stool samples by bacterial sequencing is essential.

H&O Are there any other areas of research in this field?

TG *Bifidobacterium* likely represents only the tip of the iceberg in terms of the spectrum of commensal bacteria that could impact antitumor immunity. There will likely be additional bugs that facilitate improved T-cell responses,

as well as others that are immunosuppressive and counter this effect. There are also bacteria that contribute to carcinogenesis, such as *Helicobacter pylori* in gastric cancer. All of these directions should be pursued prospectively. Analysis is completely feasible with current technologies.

Disclosure

Dr Gajewski is a member of the scientific advisory board of Evelo Biosciences.

Suggested Readings

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