MELANOMA IN FOCUS

Current Developments in the Management of Melanoma

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The Microbiome: A Basis for Novel Immunomodulation in Mice and Men

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H&O Why does immunotherapy work better in some patients with melanoma than in others?

HZ We are still unsure about that, but we are working to find a reliable way to predict which patients are most likely to respond to the various immunotherapies.

Regarding programmed death 1 (PD-1) antibodies, which are among the most successful immunotherapies to date, a previous spontaneous immune response—in particular, the presence of T-cell infiltrates in the tumor—appears to predict a response to the agent. Multiple other biomarkers of response have been proposed, including a high level of programmed death ligand 1 (PD-L1) expression, the interferon γ (IFN-γ) gene signature, and a large somatic mutation load. The IFN-γ gene signature appears to be a potential biomarker because it reflects the presence of T cells.

We are still struggling to find potential biomarkers of response to the anti–cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) agent ipilimumab (Yervoy, Bristol-Myers Squibb). One possibility may be the level of myeloid-derived suppressing cells. We still have a lot to learn about biomarkers for all these immunotherapy agents.

H&O Does the microbiome in the skin or gut of patients with melanoma differ from that in persons without the disease?

HZ We do not know yet, but we are learning a lot about the subject. The microbiome consists of the trillions of microbes that inhabit the body. We have learned how to analyze this ecosystem with next-generation sequencing. In particular, 2 landmark studies conducted in animals and published in *Science* in 2015 have shed light on the relationship between immunotherapy and the microbiome in mouse models of melanoma.

In the first study, from France, Dr Marie Vétizou and colleagues found that therapeutic antibodies targeting CTLA-4 effectively shrank tumors in mice that were populated by *Bacteroides thetaiotaomicron* or *Bacteroides fragilis*. The agents were not effective, however, in mice that were germ-free. Mice also lost their responsiveness to treatment if they were treated with antibiotics. What was exciting is that after *B fragilis* organisms had been transferred to the germ-free mice (such as with fecal transplant), the tumors were once again responsive to the anti–CTLA-4 agent. This mechanistic study provided proof that *Bacteroides* has the ability to modulate clinical response to anti–CTLA-4 antibodies in mouse models of melanoma.

In the second study, from the University of Chicago, Dr Ayelet Sivan and colleagues used syngeneic mice from 2 different facilities to study PD-1 blockade. They found that after tumor implantation, the mice from one facility were responsive to PD-1 blockade, but those from the other facility were not. Through next-generation sequencing, they learned that the main factor determining that an individual mouse would respond to PD-1 blockade was the presence of *Bifidobacterium* in the animal's digestive tract. By transferring this commensal from a responsive mouse to a nonresponsive one, they rendered the nonresponsive mouse responsive to PD-1 blockade.

Whether the observations made in the mouse

melanoma model will hold true in humans remains to be demonstrated. The relationship is going to be far more complex in humans than in transgenic mice, however. Humans have far more genetic variables than mice do, and factors such as age, sex, and environmental factors—including diet—are all known to play a critical role in modulating the gut microbiome. But currently, we do not have evidence that the microbiome of patients who respond to immunotherapy differs from the microbiome of those who do not, or that the microbiome has any effect on the development of melanoma or on how well patients respond to treatment. We must be very careful in the interpretation of these data because the complexity in humans is going to be significant.

H&O Could you discuss some of the ongoing studies in humans?

HZ It may be too soon to develop clinical trials of probiotics and anti–PD-1 antibodies because we do not know precisely whether the gut microbiome in humans modulates immune and clinical responses to cancers. It also will be critical to determine whether the bacterial commensals that may be associated with clinical responses to PD-1 blockade resemble the ones identified in mouse melanoma models. I expect, however, that there will be some significant differences between humans and mice, so it is far too soon to begin administering probiotics to patients outside clinical trials.

To evaluate the role of the gut microbiome in modulating clinical response to PD-1 blockade, we have designed a novel clinical trial in which fecal microbiota obtained from patients who are long-term responders to PD-1 blockade are transplanted to patients with disease refractory to PD-1 blockade; pembrolizumab (Keytruda, Merck) will then be administered. We want to see if we can convert nonresponsive patients into responders. We are in the process of discussing this trial with the US Food and Drug Administration (FDA) because we must obtain FDA permission before we can begin—even though gastroenterologists do not require FDA approval for the use of fecal transplants in patients with *Clostridium difficile* infection. This will be a small phase 1 trial in which 21 patients who have melanoma will initially receive standard treatment with pembrolizumab. We expect that two-thirds of the patients will not respond; these patients will then receive a fecal microbiota transplant from a long-term responder in addition to pembrolizumab. We hope to begin treating our first patient by this summer.

H&O What other studies of the microbiome are being conducted in melanoma and other solid tumors?

HZ Multiple studies have embarked on collecting stool from patients undergoing immunotherapy. Some of the preliminary data were presented at the 2017 annual meeting of the American Association for Cancer Research in Washington, DC. We need to determine whether the relationship is like that in mice, in which we have found a correlation between the presence of certain commensals and tumor response. These types of studies are being conducted in multiple cancer types. The goals are to define which bacteria aid response and to use probiotics to create an optimal environment for tumor control.

H&O What are the potential risks of these types of trials?

HZ Whenever we talk about immunotherapy, we know there is a risk for autoimmunity—perhaps less with PD-1 blockade than with CTLA-4 blockade. Checkpoint inhibitors can trigger autoimmune problems ranging from colitis to skin eruptions to various autoimmune diseases. The risk for serious side effects is relatively low with PD-1 blockade alone but higher with the combination of CTLA-4 and PD-1 blockade. Every time we spur a potent immune response, we increase the risk for autoimmunity.

In addition, fecal transplant carries a risk for infection. Before fecal transplant can be undertaken, a careful study of the donor's health and the stool itself is required, including testing for hepatitis and other viral infections.

Disclosures
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Suggested Readings

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