Gut Bacteria Influence Effectiveness of a Type of Immunotherapy

One study found that tumor samples from patients with an abundance of “good” bacteria contained a higher level of immune cells that could recognize and kill tumor cells

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The types and diversity of bacteria in the gut influence whether a patient will benefit from a type of immunotherapy used to treat cancer, according to three new studies.

The type of immunotherapy, called checkpoint inhibition, can cause even advanced tumors to shrink rapidly or disappear. Unfortunately, only a minority of patients have such strong responses to these therapies, and researchers have been trying to figure out why.

The three new studies, published January 5 in Science, all identified groups of intestinal bugs that they classified as “good” and “bad” in terms of their influence on the response to checkpoint inhibitors. People who had lots of the good bacteria were more likely to respond to these drugs. People who had little of the good bacteria—or lots of the bad bacteria—were less likely to see their tumors shrink or stop growing in response to the drugs.

Using mouse models of cancer, the researchers also found that altering the overall composition of gut bacteria, known as the gut microbiome, could affect whether tumors responded to checkpoint inhibition.

The different categories of bacteria appeared to have different effects on the immune system. Good bugs, for example, seem to prime immune cells to recognize tumor cells, whereas bad bugs seem to interfere with immune cell function.

All three studies identified different species of “good” and “bad” bacteria, and the authors suggested that human clinical trials combining treatments to alter gut bacteria with checkpoint inhibitors should be carried out.

Picking exactly which bacteria to target in trials could be tricky, cautioned Douglas Johnson, MD, an oncologist at Vanderbilt University who was not involved in any of the studies.

“But a clinical trial looking at [changing the microbiome] would be low risk for patients, and may give us some more insight into what may or may not work” to improve the response to checkpoint inhibitors, he said.

Both Good and Bad Bacteria Influence Response to Checkpoint Inhibitors

Two of the new studies focused on the composition of gut bacteria in patients with melanoma, a potentially deadly type of skin cancer.

One of these studies, funded in part by NCI, first examined stool samples taken from 42 patients with metastatic melanoma before they began immunotherapy.

The researchers, led by Thomas Gajewski, MD, PhD, of the University of Chicago, pinpointed 10 species of bacteria present in substantially different ratios between groups of patients: 8 species were more abundant in people who responded to treatment (defined as "good" bacteria), and 2 were more abundant in people who did not respond ("bad" bacteria).

A score based on the ratio of "good" to "bad" bacteria correctly identified all 16 patients who responded to one of two checkpoint inhibitors. Such a score could potentially be used as a biomarker to predict which patients might benefit from treatment, the study authors wrote.

The researchers also transplanted bacteria from patients into a type of mouse that has no gut bacteria of its own. When the researchers implanted these mice with human melanoma tumors, treatment with checkpoint inhibitors shrank tumors in mice who had received bacteria from people whose tumors had responded to the drug but not in mice that received bacteria from people whose tumors had not responded.

The team hopes to start a clinical trial this year giving patients oral doses of the most prevalent species of "good" bacteria identified in their study, called Bifidobacterium longum, explained Gajewski.

The second study, which also had NCI funding, was led by Jennifer Wargo, MD, from the University of Texas MD Anderson Cancer Center in Houston. Her group found similar results in 89 patients with metastatic melanoma. However, in these experiments, a different cluster of bacterial species made up the "good" bugs.

Patients with an abundance of these good bacteria in their guts lived longer without their melanoma progressing than did patients with less of the good bacteria.

The team also observed that people who responded to checkpoint inhibition had a more diverse mix of bacteria in their gut microbiomes than the non-responders.

In follow-up laboratory work, the researchers found that tumor samples from patients with an abundance of "good" bacteria contained a higher level of immune cells that could recognize and kill tumor cells, whereas tumors from patients with more "bad" bacteria contained cells that could suppress the immune response, which renders immunotherapy ineffective.

Similar to the University of Chicago study, the MD Anderson team also implanted human melanoma tumors into mice that had received gut bacteria from patients. Mice receiving the

“good” bacteria from patients responded to checkpoint inhibition, while those that received the “bad” bacteria did not.

The third study, led by Laurence Zitvogel, MD, from the Gustave Roussy Cancer Campus in France, identified yet another set of “good” bacteria in patients with advanced lung, kidney, or bladder cancer.

The European study also highlighted the potentially harmful effects that antibiotics can have on the gut microbiome. Patients who had taken antibiotics for an infection within 2 months before or 1 month after starting immunotherapy with checkpoint inhibitors did not live as long as patients who didn’t take antibiotics, they found.

Manipulating the Microbiome

“An important and clinically relevant issue is whether manipulation of the intestinal microbiome could turn patients [who] are nonresponsive to immune checkpoint blockade into responders,” wrote Christian Jobin, PhD, of the University of Florida, in an editorial that accompanied the three research articles.

“These studies report a fascinating interaction between intestinal bacteria and antitumor efficacy of [immune checkpoint inhibition] in patients,” suggesting that tweaking individual patients’ microbiomes has potential to modify the effects of these immunotherapy drugs, Jobin continued.

Other factors besides the microbiome are also known to affect whether immunotherapy works, explained Johnson. For example, he said, the immune system seems more likely to recognize and target tumors with a greater number of genetic mutations.

Research studies testing many different ways to improve responses to immunotherapy are currently underway, he added. These include testing new drugs that stimulate the immune cells that recognize tumors and drugs that suppress cells that can dampen the immune response.

So, in addition to manipulating the microbiome, “there’s a whole host of other approaches that have also shown promise. And I don’t think these things are mutually exclusive, and may ultimately prove complementary,” Johnson concluded.

Immune Cells May Be the Important Players in Immunotherapy Response

Two new studies, published February 1 in the Journal of Clinical Investigation, hint that a patient’s immune cells may play a much more important role in the response to a type of immune checkpoint inhibitor than do tumor cells themselves.

In one study, researchers from the University of Texas Southwestern Medical Center in Dallas, found that, in mouse models, whether tumor cells expressed the protein targeted by the therapy

was largely irrelevant in predicting whether the drug worked.

Instead, it appeared to be the presence of the drug's target on immune cells called myeloid cells that seemed to determine whether tumors shrank in response to the treatment.

The second study, from researchers at the University of Michigan, found similar results in mouse models of cancer. And when the researchers looked at tissue samples from patients with melanoma or ovarian cancer who had been treated with the same type of checkpoint inhibitor, they found that almost 75 percent of patients had expression of the drug's target only in non-tumor cells. The higher the expression of the drug's target in the immune cells, the more likely patients were to have responded to the drug.

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