Can Fecal Transplants Improve Response to Immunotherapy?

Altering gut bacteria may help overcome resistance to checkpoint inhibitors in people with melanoma and other cancers.

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Using stool transplants to alter the gut microbiome may turn cancer patients who do not respond to checkpoint inhibitor immunotherapy into responders, according to a pair of studies recently published in Science magazine.

“Our study is one of the first to demonstrate in patients that altering the composition of the gut microbiome can improve the response to immunotherapy,” Giorgio Trinchieri, MD, chief of the National Cancer Institute (NCI) Laboratory of Integrative Cancer Immunology and coauthor of one of the studies, said in an NCI press release. “The data provide proof of concept that the gut microbiome can be a therapeutic target in cancer.”

A growing body of evidence shows that the gut microbiome—the ecosystem of bacteria and other microorganisms in the intestines—plays a key role in health and disease, including the immune response. Some beneficial microbes release metabolic by-products that enhance immune cell activity and suppress inflammation, while harmful bacteria can lead to a leaky gut that triggers an inflammatory response.

In 2017, researchers showed that advanced melanoma patients with more diverse gut bacteria responded better to PD-1 checkpoint inhibitors, such as Keytruda (pembrolizumab) and Opdivo (nivolumab), which restore T-cell activity. People with a favorable gut microbiome had more active T cells in their tumors and longer progression-free survival. Other researchers have seen similar associations in people with bladder, lung, kidney and liver cancer and in mice with pancreatic cancer.

Such research raised the possibility that altering the gut microbiome could improve treatment response. One way to do this is with prebiotics (undigestible plant fiber) or probiotics (foods or supplements that contain live bacteria). But off-the-shelf probiotic supplements appeared to actually make matters worse, reducing microbial diversity and lowering immunotherapy response. On the other hand, people who ate more fiber had a better response.

Another way to change the gut microbiome is by administering fecal microbiota transplants (FMT)

using “poop capsules” or enemas containing intestinal bacteria from healthy donors or cancer patients who respond well to treatment. Early studies showed that mice that received fecal transplants from cancer patients with good responses had greater T-cell activity and slower cancer growth. That set the stage for testing this approach in humans.

In the first report, Diwakar Davar, MD, and colleagues at the University of Pittsburgh Hillman Cancer Center, along with Trinchieri and collaborators at the NCI, described results from a Phase II trial (NCT03341143) that included 16 advanced melanoma patients who initially did not respond to Keytruda or Opdivo used alone or in combination with other therapies.

The participants received a single stool transplant, administered via colonoscopy, from donors who responded well to checkpoint inhibitor immunotherapy and then were started on Keytruda, several of them for the second time.

Six of the 15 evaluable patients experienced tumor shrinkage or stable disease. One participant was still responding more than two years later, and four others were still on treatment with no further disease progression for over a year.

In these responders, gut bacteria composition rapidly shifted toward more favorable types associated with checkpoint inhibitor response, T-cell activation and a reduction in myeloid cells and cytokines (including interleukin 8) linked to immune cell suppression and immunotherapy resistance. These changes persisted unless the microbiome was disturbed—for example, by use of antibiotics.

Fecal transplants “changed the gut microbiome and reprogrammed the tumor microenvironment to overcome resistance” to PD-1 checkpoint inhibitors in a subset of people with advanced melanoma, the researchers concluded.

“The likelihood that the patients treated in this trial would spontaneously respond to a second administration of anti-PD-1 immunotherapy is very low,” study coauthor Hassane Zarour, MD, said in a University of Pittsburgh press release. “So any positive response should be attributable to the administration of fecal transplant.”

Treatment responders had an increase in certain broad families of bacteria and a decrease in others, but the researchers have not yet pinpointed particular beneficial species.

“FMT is just a means to an end,” Davar said in the press release. “We know the composition of the intestinal microbiome—gut bacteria—can change the likelihood of responding to immunotherapy. But what are ’good’ bacteria? There are about 100 trillion gut bacteria and 200 times more bacterial genes in an individual’s microbiome than in all of their cells put together.”

In the second report, Erez Baruch, MD, and Ben Boursi, MD, of Tel Aviv University in Israel, and colleagues described findings from a smaller Phase I trial that included 10 people with metastatic melanoma who did not respond to PD-1 checkpoint inhibitors. Fecal microbiota transplants led to favorable changes in immune cell populations and gene expression both in the gut lining and in

the tumor microenvironment. After receiving transplants and restarting immunotherapy, two patients had partial responses and one experienced complete remission.

Fecal transplants were well tolerated in these studies. The procedure, commonly used to treat recurrent Clostridium difficile infections, is generally safe; however, the Food and Drug Administration warned last year that in rare cases it can lead to serious infections.

Davar's team plans to expand their melanoma trial and start a larger study of fecal transplants for people with kidney, lung and other types of cancer. They ultimately aim to use oral capsules containing a cocktail of selected beneficial microbes, although that is likely several years away.

"We expect that future studies will identify which groups of bacteria in the gut are capable of converting patients who do not respond to immunotherapy drugs into patients who do respond," said study coauthor Amiran Dzutsev, MD, PhD, of NCI's Center for Cancer Research. "These could come from patients who have responded or from healthy donors. If researchers can identify which microorganisms are critical for the response to immunotherapy, then it may be possible to deliver these organisms directly to patients who need them, without requiring a fecal transplant."

Added Zarour, "Even if much work remains to be done, our study raises hope for microbiome-based therapies of cancers."

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