Can patients’ gut microbes help fight cancer?

A healthy gut microbiome seems to be required for immuno-oncology therapies designed to turn up the body’s immune response to attack tumors. Researchers have many “black boxes” to fill in on how gut microbes directly or indirectly influence the T cells unleashed by immune checkpoint inhibitor therapies. But several groups are betting that microbiome-based therapies can help more patients respond to immunotherapies and become one of the biggest breakthroughs in cancer treatment in decades. By Kendall Powell

At first glance, it might seem odd that our gut microbiome plays an influential role in our immune system response. It’s not so strange, though, considering that the vast majority of our immune cells, up to 70%-80% of them, hang out in the intestine regularly. There, in the great “transit hub” of the body, they are directly exposed to the outside world and to the incredible genetic diversity of our gut microbes. Made up of trillions of mostly bacterial cells, the microbiome pumps out metabolites as it goes about its daily business of aiding digestion and helping synthesize vitamins and other nutrients. Roving immune cells ensure that “good” microbes and the body’s cells are tolerated while invaders get rooted out.

Although the molecular details are far from being completely understood, it’s become clear that having a healthy gut microbiome ensures that T cells are broadly primed against antigens and activated into cytotoxic CD8+ T cells that infiltrate and attack tumor cells. Advances in immune checkpoint inhibitor (CPI) therapies have shown that sometimes, when the checkpoints, or brakes, are taken off the cytotoxic T-cell responses, even metastatic tumors can be shrunk and controlled. However, oncologists have been frustrated to find that only a minority of patients—typically less than 30%-40%—respond to CPI therapies.

Now, research is showing that when combined with CPI therapies, such as anti-PD-1, anti-PDL1, and anti-CTLA-4 immunotherapies, a healthy, diverse gut microbiome results in better patient responses. Figuring out which microbes—or which metabolites or products—are shaping these immune responses has become a competition among researchers in the field. But these “microbe managers” are hopeful they can find ways to nudge, sway, or push patient microbiomes to energize their tumor-fighting T cells and convert more patients into CPI responders.

“There’s an emerging body of literature appreciating the role of the intestinal microbiota in calibrating systemic immune responses,” says Alexander Khoruts, director of the Microbiota Therapeutics Program at the University of Minnesota in Minneapolis. He was among a pioneering group of gastroenterologists that first used fecal microbiota transplants (FMTs) to treat patients with recurrent Clostridiodes difficile infections.

Uncovering the gut-cancer connection

In 2013, Laurence Zitvogel and her group at the Gustave Roussy Cancer Campus in Villejuif, France, concluded that mice with missing or depleted gut microbiomes had a weaker immune response to chemotherapy than mice with intact microbiomes did (1).

It was such a novel idea that it immediately drew skepticism. Bernat Olle, CEO of Vedanta Biosciences in Cambridge, Massachusetts, recalls thinking at the time, “Hmm, I don’t know if I believe that.” Cancer has been thought of as a disease of the genome and accumulating mutations, he says. “But, we now know that cancer is also a disease involving an ineffective immune response.”

Work by Zitvogel’s group in 2015 convinced Olle and kicked off this field. When they treated sarcomas in mice with ipilimumab, they found that the CPI could control the tumors in pathogen-free mice, which have normal gut microbiomes, but not in germ-free mice, which have no gut microbiome (2). The clincher was that transferring beneficial species of bacteria back into these mice restored the anticancer activity of the CPI.

Vedanta’s scientific cofounder, Kenya Honda, a team leader at RIKEN Center for Integrative Medical Sciences in Saitama, Japan, discovered that the induction of CD8+ cytotoxic T cells happens in the intestine and depends on the microbiome’s presence (3). “Obviously, my first reaction to Zitvogel’s initial discovery was wrong,” says Olle. Just 10 years ago, he recalls, we used to think that the immune system’s function was to tell the difference between self and nonself. But Olle believes that its role should now be considered as broader—it performs triage, making quick decisions on who to attack and who to tolerate. “Maybe the immune system is more like a gardener in the human body,”
deciding which weeds must be pulled and thrown out and which can stay in the lawn."

Since the Zitvogel group’s initial discovery, many studies have shown that patients who receive a broad range of antibiotics known to diminish gut microbiota do not respond well to CPIs (4, 5) and have worse adaptive immune responses to vaccines (6).

One of the microbiome’s potential mechanisms for influencing T cells, and therefore cancer immunotherapy, is through the vast number of gut metabolites that can act as immune-modulating signals. "T cells can get their education from the bacteria in the intestine, and then are circulated out to the rest of the body multiple times per day," says Olle. "What happens in the intestine affects the entire immune system."

**Black boxes between microbes and T cells**

How exactly these interactions unfold between microbes, their metabolites, T cells, and other immune cells remains largely a mystery.

"Having certain bacteria present influences the balance of activated, cytotoxic CD8\(^+\) T cells," says Sarah Highlander, microbial genomic scientist at the Translational Genomics Research Institute in Flagstaff, Arizona.

But researchers still need to identify which beneficial bacteria must be present, and how they molecularly switch on T cells. Highlander and her collaborator, Sumanta Pal, a medical oncologist at City of Hope cancer center in Duarte, California, have longitudinally tracked the microbiomes of patients undergoing anti-PD-1 CPI therapies.

They found that metastatic renal-cell carcinoma patients who responded to CPIs had more diverse microbial diversity and an increasing abundance of Akkermansia muciniphila in particular (7), as compared to nonresponders.

In Pal’s mind, gut epithelial response to certain neighboring microbes by secreting inflammatory cytokines, which then influence the activation of T cells. This is how Olle envisions the process, too. Vedanta has shown that its commensal bacteria mix must be alive—and therefore producing metabolites—and signals to be effective.

But there are many steps along this pathway where the mechanism is unknown: Are microbes directly or indirectly signaling to T cells? What other types of T cells (helper T cells? T regulatory cells?) does the microbiome influence? Once T cells are fully activated in the gut, how do they find their way to and infiltrate tumors?

One reason there are several black boxes between what the microbes are producing and what exact population of T cells become activated, is that extracting those T cell populations from human patients and studying them is extremely difficult, Khoruts explains.

Another camp of researchers takes that theory one step further, arguing that among the flood of microbial products found in the gut, some might mimic tumor antigens and more directly create a tumor-directed population of T cells.

“We believe the intestine is a reservoir for T cells that can recognize bacterial antigens that mimic tumor antigens,” says Christophe Bonny, chief scientific officer at Enterome in Paris, France.

**Microbiome-based drugs**

Now, the race is on to develop and test microbiome-based approaches designed to convert a cancer patient into a CPI responder.

“That’s the holy grail,” says Highlander. "Adding a mix of bugs, in a pill form, to transform a patient into a good CPI responder." She predicts there may be many successful products that fulfill this goal. "We know from the Human Microbiome Project that people can have very different microbiome community compositions, but they are functionally the same."

She is involved in testing a combination therapy of CBM588, a crystallized form of Clostridium butyricum, alongside CPI treatment. This bacterium produces butyrate, a short-chain fatty acid thought to enhance the growth of certain Bifidobacteria, one of the groups found in responders’ microbiomes.

Vedanta Biosciences has developed VE800, a purified, freeze-dried mix of 11 bacterial strains based on Honda’s work that can activate interferon-gamma-producing cytotoxic T cells (3). It is being tested in combination with the CPI nivolumab in patients with advanced colorectal cancer, gastric cancer, and melanoma. During the trial, Vedanta plans to sequence patient stool samples to see whether and to what degree the VE800 strains colonize the gut.

**Seres Therapeutics** in Cambridge, Massachusetts, is testing another bacterial consortia drug candidate, SER-401, in metastatic melanoma patients in combination with nivolumab. SER-401, which contains strains fractionated and purified from healthy human donor stool, will be given daily over 8 weeks, starting before the CPI course and continuing alongside it. The design of the drug is based on a collaboration with Jennifer Wargo at MD Anderson Cancer Center in Houston, Texas, which revealed key signatures of strains associated with CPI response, including bacteria from the Ruminococcaceae family (8), says Matthew Henn, executive vice president and CSO at Seres.

Khoruts and the Microbiota Therapeutics Program are testing an "FMT in a pill" formulation called MTP101, in combination with the CPI...
durvalumab, to treat non-small cell lung cancer. In contrast to the Vedanta and Seres candidates, MTP101 is a whole microbiome purified and freeze-dried from healthy donor fecal material.

Khoruts concedes that trials like his, using an FMT-like whole-microbiome pill, should happen in parallel with the other approaches that have narrowed down to a handful of strains. “We can all learn from each other [and] from the data,” Khoruts says.

Whether encapsulated bacterial mixtures will actually colonize a cancer patient’s gut is an open question, says Ryan Weight, medical oncologist at the University of Colorado Anschutz Medical Campus in Aurora. This is also true for other types of patients—no “FMT in a pill” products have yet to be proven to colonize human guts, and it is still up for debate exactly how FMTs in C. difficile infection patients shift their gut microbiota over time.

“All of these belong to a class of therapeutics that physicians haven’t used yet,” says Khoruts, adding that it’s an entirely new area of pharmacology to assess these drugs’ formulation, dosing, fate in the body, and pharmacodynamics.

Khoruts points out that these approaches are very also different from using FMTs to treat C. difficile because those patients’ native microbiomes have been nearly wiped out by heavy-duty antibiotics. That’s akin to having a field decimated by herbicides and fertilizers and expecting it to grow a healthy crop. Cancer patients typically still have their own indigenous, intact microbiome, which is more like an established prairie that an oncologist is trying to Overseed with some beneficial species.

It could also be true that different tumor types might need different bacterial species in the gut to activate T cells against those specific tumors, says Weight. “By 2040, we might be in a place where we have probiotic cocktails directed against colon cancer.”

Mining the microbiome for antigens

Enterome is taking an altogether different approach, based on the idea of tumor antigen mimics. Recently, the company and its collaborators published 20 million genes from sequencing more than 8,000 people’s gut microbiomes, representing more than 4,600 species of microbes (9).

“The beauty of the microbiome is that digging into this pool of 20 million gene products is like going into the Amazonian jungle to look for drugs among all the biodiversity there,” says Bonny.

To winnow down which of the 20 million bacterial products might be responsible for the immune responses in CPI responder patients, Enterome ran several bioinformatics filters on the dataset to get to a “short list” of 20,000 proteins. These were small, secreted molecules resembling cytokines, chemokines, or hormones that were likely to interact with human cell receptors.

Next, Enterome fished among those bacterial peptides to look for molecules that resembled specific tumor antigens, such as IL-13Ra2, which is uniquely expressed by glioblastoma tumors. Enterome identified three bacterial antigens to put into its vaccine product EO2401, in hopes of awakening T cells that recognize these antigens.

In testing, glioblastoma patients receive a vaccination shot every 3 weeks during the first couple of months of their CPI course of treatment. “If we are correct, we are targeting memory T-cell populations that have already seen these microbial antigens,” says Bonny. “So we expect it to be fast.”

Promise amidst potential pitfalls

Work in this field in the last five years has shown that oncologists “need to pay attention to how this complex interplay comes into effect in treating our patients,” says Weight. In his practice, that means advising patients against taking antibiotics if possible in the 6-8 weeks before starting CPI therapies, and surprisingly, also advising them against taking over-the-counter probiotics at this stage. According to Weight, there’s no evidence of probiotics increasing the efficacy of CPI therapies, and in fact, these highly selected strains could pose a risk of disrupting a patient’s natural microbiome which can be protective, he says.

Pal also cautions that researchers need to better understand how the microbiome is influencing immunotherapy. “Before we give a product fortifying Akkermansia in patients, we need to know that it’s really Akkermansia that is a key player,” he says.

Researchers have many questions left to answer in this incredibly complex space.

“Immuno-oncology has been a huge breakthrough in cancer research,” says Khoruts, noting that former President Jimmy Carter is alive because of CPI therapy. He notes that the microbiome-oncology field is at very early stages, with many different ideas to pursue and candidates to put through testing.

“Even in the best cases, only 40% of patients respond to CPIs,” he says. “There is a lot of room for us as a field to make that percentage better.”

References

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