CANCER

Gut microbes shape response to cancer immunotherapy

Planned trial will manipulate patients’ microbiomes

By Jocelyn Kaiser

When scientists reported 2 years ago that mice with certain gut bacteria responded best to a powerful new type of cancer drug, other researchers were intrigued but cautious—mice, after all, aren’t humans. But this week, two teams offer a raft of evidence from cancer patients suggesting that the gut microbiome—the community of bacteria, viruses, and other bugs living in our digestive tracts—helps determine whether tumors shrink when treated with immunotherapy drugs.

The studies, which appear online in Science, track responses to a type of immunotherapy known as a PD-1 inhibitor. “These are the best-done and largest assessments of how the microbiome may influence therapeutic outcome” from those drugs, says immunotherapy researcher Jeffrey Weber of New York University in New York City, who was not involved in the studies.

PD-1 inhibitors fight cancer by blocking a “checkpoint” molecule on immune cells called T cells, which tumors use to shut down the immune cells. Checkpoint inhibitors have had remarkable results, holding certain cancers at bay for years. But only about 25% of all patients respond to PD-1 blockers.

In a 2015 Science paper, a team led by immunologist Laurence Zitvogel of the Gustave Roussy Cancer Campus in Villejuif, France, reported that changing the gut microbiome of a mouse could make its tumors respond better to a checkpoint blocker. Another group reported that different gut microbes seemed to explain why mice from two separate suppliers responded differently to PD-1 blockers.

In one of the new papers, Zitvogel’s team then looked for differences in the gut bacteria of patients who did or did not respond well. In the responders, they fingered Akkermansia muciniphila, a species associated with the gut’s mucus lining. When germ-free mice with no gut bacteria received fecal transplants from responders, they did better on PD-1 blockers than did mice given nonresponder feces. And poorly responding mice could be turned into responders by feeding them A. muciniphila.

The gut microbiome also matters in melanoma patients receiving PD-1 blockers, a team led by Jennifer Wargo of MD Anderson Cancer Center in Houston, Texas, reports in the other paper: Responders had a more diverse microbiome and more of specific bacteria. Her group also found that giving mice fecal transplants from patients who did or did not respond to the drugs led to similar outcomes in the animals.

The good bacteria seem to help the drugs by priming T cells, which Wargo’s group reported were more abundant in the gut and tumors of the mice who got fecal transplants from responder patients. Zitvogel’s team found that a specific immune signaling molecule, or cytokine, called IL12 that is released in response to A. muciniphila may help rally the T cells. They “are educated by the good bugs that you have added,” she says.

The new studies have “tremendous implications,” Wargo says. For one, Zitvogel figures that simply avoiding antibiotics while taking PD-1 blockers could boost patient responses from the current 25% to 40%. And Wargo is planning to test whether manipulating the gut microbiome with fecal transplants (in pill form) or a bacterial treatment could help more melanoma patients respond to PD-1 blockers. The trial, sponsored by the Parker Institute for Cancer Immunotherapy in San Francisco, California, could begin in 6 to 8 months. Immunotherapy researcher Alexandra Snyder of Memorial Sloan Kettering Cancer Center in New York City agrees that although planning rigorous clinical trials will be “complicated,” it’s time to move ahead.

Conservationists say the highest priority is to protect the remaining population, which persists in about 1100 square kilometers of forest. In 2014, the government protected most of the forest from logging. But the best habitat—about 7 square kilometers of lowland forest—is not protected, and villagers sometimes kill orangutans that raid gardens. Gold mining is also driving deforestation.

A planned hydropower dam is the latest threat. The so-called run-of-river design would not store much water behind a dam, but would require digging a long tunnel in an area that holds the densest population of orangutans. An access road would promote deforestation, Fredriksson says, complicating plans to use forest corridors to reconnect the four blocks of orangutan habitat.

A vulnerable home

The Tapanuli orangutans face many threats, including fragmented habitat, gold mining, and a planned dam.
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Science 358 (6363), 573.
DOI: 10.1126/science.358.6363.573