Study reveals how diet and probiotics boost melanoma immunotherapy response

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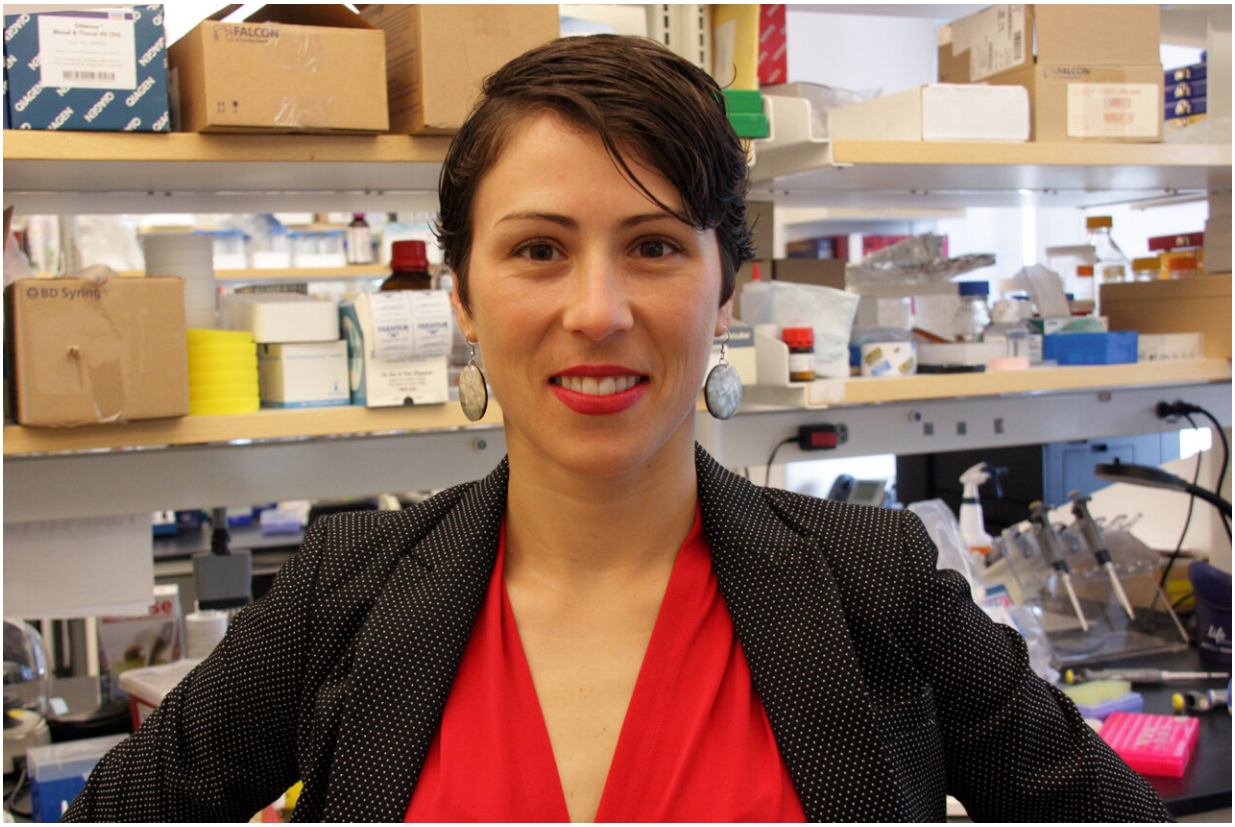

Marlies Meisel, Ph.D., assistant professor in the Department of Immunology at the University of Pittsburgh School of Medicine and member of the Cancer Immunology and Immunotherapy Program at UPMC Hillman Cancer Center. Credit: Marlies Meisel

In mice with melanoma, probiotic bacteria travel from the gut and

establish in tumors, where they directly stimulate immune cells to make cancer immunotherapy more effective, according to a new study led by University of Pittsburgh researchers.

Published today (April 6) in *Cell*, the study showed that Lactobacillus reuteri stimulates cancer-killing T cells by secreting a compound called indole-3-aldehyde, or I3A. When the researchers gave mice a diet rich in the amino acid tryptophan—which the bacteria convert to I3A—immunotherapy drugs had a stronger effect on restraining tumor size and prolonging survival. The findings lay the groundwork for clinical trials to test whether I3A treatments or combining probiotics and diet could improve outcomes in melanoma patients undergoing immunotherapy.

"We knew that gut microbes influence immunotherapy response, but there were still big questions about how they do this and whether they act from the gut or if they have to be at the tumor site," said senior author Marlies Meisel, Ph.D., assistant professor in the Department of Immunology at Pitt's School of Medicine and member of the Cancer Immunology and Immunotherapy Program (CIIP) at UPMC Hillman Cancer Center. "Our study is the first to show that orally administered bacteria increase efficacy of cancer immunotherapy by moving to tumors outside of the gut where they directly impact immune cells in the tumor."

The gut microbiome is an important factor in why immunotherapy—which helps the body's immune system recognize and kill cancer cells—is effective for some patients but not others. Several recent studies have also found a link between probiotic supplements and immunotherapy response in melanoma patients.

To learn more, Meisel and her colleagues fed L. reuteri, a bacterium that is often part of commercially available probiotics, to germ-free mice

with melanoma. They showed that the bacteria moved from the gut to tumors, where they established and persisted over time.

Compared to control mice that did not receive bacteria, those given L. reuteri had greater quantities of more potent CD8, or "killer," T cells at the tumor site, the tumors shrank more, and the mice lived longer.

And the effects of L. reuteri weren't limited to melanoma. In mouse models of adenocarcinoma, fibrosarcoma and breast cancer, the bacterium similarly moved to tumors beyond the gut and suppressed cancer growth.

Delving deeper, the researchers showed that L. reuteri stimulates immunity in tumors by producing I3A, which activates a receptor in CD8 cells. Although the receptor is found in almost every cell in the body, I3A acts specifically on CD8 cells to enhance their cancer-killing abilities. When the researchers removed the receptor within these cells, the bacteria no longer induced anti-tumor immunity, showing that the effect is dependent on this receptor in CD8 T cells. Using a genetically modified strain of L. reuteri that can't produce I3A, they demonstrated that this compound is essential for the bacterium's effect on enhancing anti-tumor immunity and tumor suppression.

"While the microbiome of tumors beyond the gut, including melanoma, had been described, the concept that tumor microbes play an active role in mediating cancer immunotherapy efficacy had not been demonstrated," said Meisel. "So, we were surprised to find that I3A released by L. reuteri within the tumor enhanced immunotherapy response whereas the presence of L. reuteri in the gut was insufficient to have an anti-tumor effect."

To see whether I3A could play a role in human response to immunotherapy, Meisel teamed up with Diwakar Davar, M.D., assistant

professor of medicine at Pitt and member of the CIIP, and Hassane Zarour, M.D., professor of medicine at Pitt and co-leader of the CIIP. Previously, they found that modifying gut bacteria via fecal transplants improved immunotherapy response in melanoma patients.

Analyzing blood samples from melanoma patients undergoing immune checkpoint inhibitor treatment, the researchers found that patients who responded well to immunotherapy had elevated I3A levels. Higher levels of I3A before treatment were also associated with a better chance of survival.

"Building on these findings in the future, it might be possible to use I3A levels as a biomarker to predict which patients are likely to respond to immunotherapy," said Meisel. "Another direction I'm excited about is developing clinical trials to evaluate whether combining I3A with immunotherapy could improve outcomes for patients."

L. reuteri requires tryptophan—an amino acid found in foods such as chicken, soybeans, oatmeal, nuts and seeds—to make I3A. When mice with melanoma ate a tryptophan-rich diet, tumors grew more slowly, and the mice lived longer than control mice fed an otherwise identical diet that was low in tryptophan. A diet high in tryptophan also enhanced the effect of immunotherapy on shrinking tumors.

Meisel cautioned that more research, including well-controlled clinical trials, is needed to understand whether a tryptophan-rich diet could influence outcomes in cancer patients.

"This paper shouldn't serve as a recommendation, but as an initiation: We hope it will spark other studies that investigate how diet affects immunity and cancer outcomes," she said. "My lab is interested in understanding whether holistic approaches, such as diet or lifestyle changes, could enhance the efficacy of immunotherapy and other cancer

treatments. I think it's empowering for patients that they could make these changes themselves—of course, after careful clinical consideration—and have some control over their treatment journey, rather than being entirely at the mercy of the health care system."

More information: Dietary tryptophan metabolite released by intratumoral Lactobacillus reuteri facilitates immune checkpoint inhibitor treatment, *Cell* (2023). www.cell.com/cell/fulltext/S0092-8674(23)00271-4

Provided by University of Pittsburgh