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Gut Bacteria Are Linked to Success of Cancer Treatment

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The new studies could pave the way for anti-cancer therapies that control the makeup of these bacterial communities.

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Michelle Hampson (http://www.aaas.org/person/michelle-hampson) [1]

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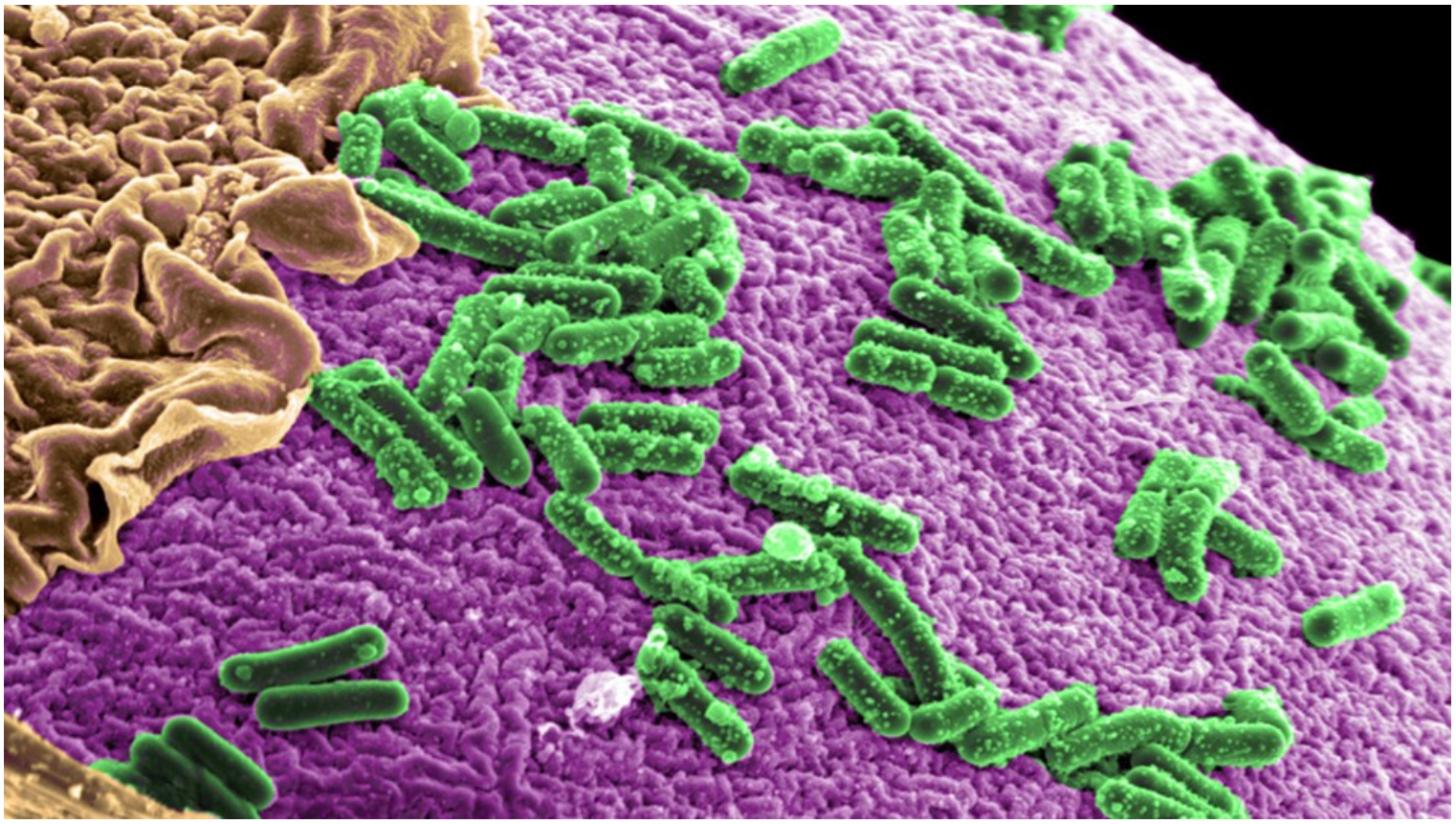

The overall collection of bacteria in the human gut may determine how a cancer patient responds to immunotherapies. | Flickr/ Pacific Northwest National Laboratory (https://www.flickr.com/photos/pnnl/8146322408) [5]/ CC BY-NC-SA (https://creativecommons.org/licenses/by-nc-sa/2.0/) [6]

Two new studies hint that the beneficial bacteria living in our gut could be the reason why some people respond better than others to immunotherapy, a potentially highly effective form of cancer treatment.

The immune system is a network of cells and organs throughout the body that protect it from disease, and immunotherapies that boost this natural defense system have shown success in treating skin, lung, and head and neck cancers. However, researchers have been unable to determine why immunotherapy can cause very different immune responses from one patient to the next. The two studies published in the 5 November issue of *Science* could help resolve part of this mystery.

Recent research has shown that the community of bacteria in our guts can affect functions of other parts of the body. This led Thomas Gajewski of the University of Chicago and his colleagues to explore whether this gut microbiota may be contributing to the different responses to immunotherapy in cancer patients.

The researchers studied (http://www.sciencemag.org/lookup/doi/10.1126/science.aac4255) [7] the effects of anti-PD-1/PD-L1 monoclonal antibodies, an immunotherapy used to treat skin cancer, on two different groups of mice called JAX and TAC, each with its own distinctive set of gut microbes.

The JAX mice responded well to the immunotherapy, with many of their tumors shrinking completely. The TAC mice responded less favorably and their tumors continued to grow quickly. However, the researchers found that they could slow TAC tumor growth by transferring JAX fecal matter — with its unique load of microbes — into the guts of TAC mice.

JAX mice have 400 times more *Bifidobacterium* microbes residing in their guts compared to TAC mice, the researchers found, and the presence of these bacteria was directly related to the effectiveness of the immune system to target cancerous cells. Further investigation revealed that *Bifidobacterium* boost the ability of some cells to initiate an immune response against tumors.

"It's also important to recognize that only certain species of *Bifidobacterium* have this effect, and that it is not yet clear which commensal bacteria might have a similar effect in humans," said Gajewski. "But nevertheless, it was exciting and unexpected that we could identify bacteria that could be used as a therapeutic after tumors were already growing."

Marie Vetizou at the Institut de Cancérologie Gustave Roussy Cancer Campus and colleagues found a similar relationship between gut microbes and response to anti-cancer treatment. In their study (http://www.sciencemag.org/lookup/doi/10.1126/science.aad1329) [8] of the immunotherapy agent ipilimumab, the researchers found that tumors in mice with no microbes in their gut did not respond to the treatment.

Their analysis revealed that just a single dose of ipilimumab can cause a decrease of the species *Bacteroidales* and *Burkholderiales*. Replenishing these species in microbe-free mice restored the anti-cancer effects of ipilimumab treatment.

Results in mice can sometimes be different than in humans, so the researchers also studied ipilimumab's effects in 25 patients living with advanced skin cancer. They found that the immunotherapy changed the dominant kind of gut microbe found in the patients. When they transferred gut microbes from the treated humans to mice, they found that mice with higher amounts of transplanted *Bacteroides fragilis* responded better to ipilimumab treatment compared to mice with less of the microbe present.

Collectively, these two studies demonstrate that the gut microbiome could play an important role in facilitating immunotherapy for cancer. Gajewski's team aims to explore this relationship further by taking samples of gut microbes from patients who are being treated with immunotherapy. This may help the scientists identify species of bacteria that are associated with better clinical outcomes.

"The deeper molecular mechanisms of these effects also need to be solved," Gajewski said. "Ultimately, we hope to be able to manipulate the microbiota to our therapeutic advantage in cancer patients."

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