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Gut bacteria can dramatically amplify cancer immunotherapy

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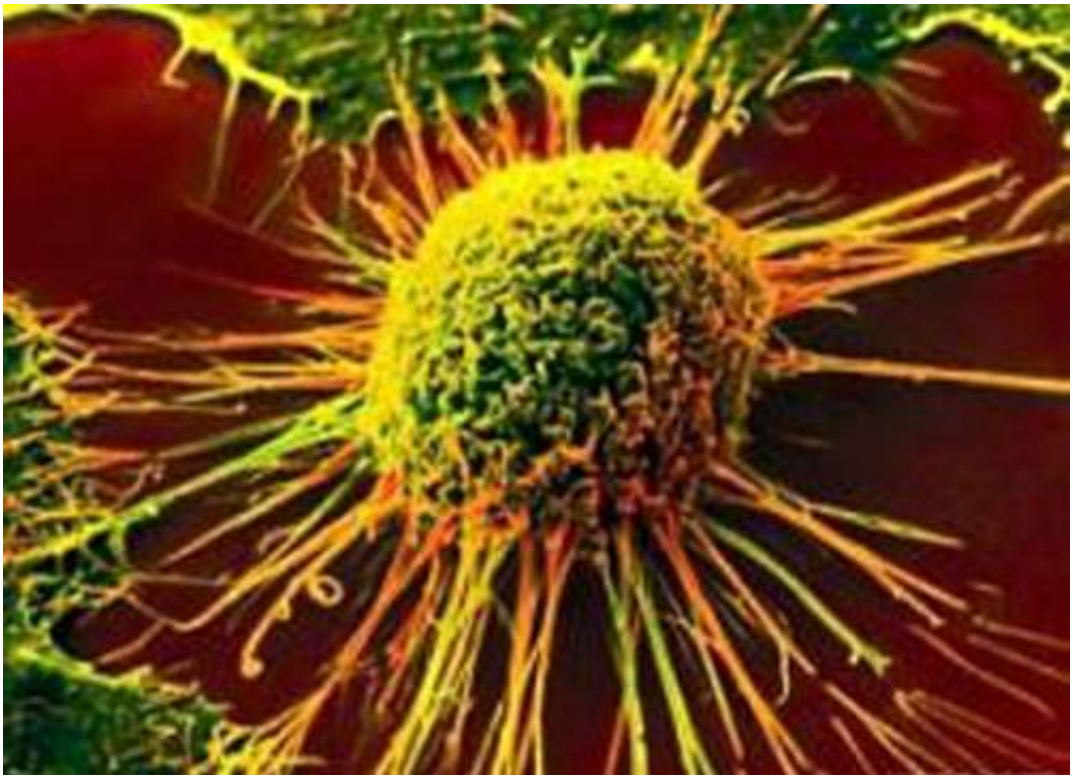

By introducing a particular strain of bacteria into the digestive tracts of mice with melanoma, researchers at the University of Chicago were able to boost the ability of the animal's immune systems to attack tumor cells. The gains were comparable to treatment with anti-cancer drugs known as checkpoint inhibitors, such as anti-PD-L1 antibodies.

The combination of oral doses of the bacteria and injections with anti-PD-L1 antibody nearly abolished tumor outgrowth, the researchers report online Thursday in the journal *Science*.

"Our results clearly demonstrate a significant, although unexpected, role for specific gut bacteria in enhancing the immune system's response to melanoma and possibly many other tumor types," said study director Thomas Gajewski, MD, PhD, professor of medicine and pathology at the University of Chicago.

"The field has recently recognized close connections between the gut microbiome and the immune system," he said. "This finding provides a novel way to exploit that connection, to improve immunotherapy by selectively modulating intestinal bacteria."

Checkpoint inhibitors such as ipilimumab, nivolumab and pembrolizumab have had a dramatic impact on treatment of several tumor types, including melanoma, lung cancer, head and neck cancers and others. But only a minority of patients—one-third or less—have a vigorous response. Cancer researchers have wondered why so few benefit.

Gajewski and colleagues found a similar pattern in the mice they use for cancer research. They noticed that mice purchased from Jackson Laboratory (JAX) tended to have a robust spontaneous immune response to small melanoma tumors implanted under their skin. Mice from Taconic Biosciences (TAC) showed only a weak immune response.

But when the researchers put the mice from both sources in cages together for three weeks, they found that co-housing "completely abolished the differences in tumor growth," Gajewski said. This made them suspect that by sharing exposure to various types of bacteria, the TAC mice had acquired microbes from JAX mice that somehow

enhanced their immunity to tumors.

They confirmed their suspicion by collecting fecal matter from JAX mice and transferring it into the stomachs of TAC mice. It worked. Treated TAC mice were then able to mount a strong immune response and delay tumor growth. The reverse process, transferring fecal bacteria from TAC to JAX mice had no effect.

Next, they compared the effects of bacterial transfer against a checkpoint inhibitor, anti-PD-L1 antibodies. They found that introducing the bacteria was just as effective as treating them with anti-PD-L1 antibodies, resulting in significantly slower tumor growth. Combining the benefits associated with the bacteria with anti-PD-L1 treatment dramatically improved tumor control.

So they began searching for the specific bacteria that made the difference. They identified microbes from the digestive tracts of JAX and TAC mice by large-scale sequencing. Although there were significant differences in 254 taxonomic families of bacteria from the two sets of mice, three groups were prominent.

When they tested the effects of each group on the mice's immune systems, one group, the Bifidobacterium, stood out. Within two weeks of oral administration, TAC mice that received just Bifidobacterium species had a marked increase in the anti-tumor T cell responses.

Mice treated just with Bifidobacterium, rather than the full fecal transfer, displayed tumor control comparable to those who received the full mixture. The effect was long-lasting. TAC mice exposed to tumors as late as six weeks after the Bifidobacterium transfer were still able to mount a robust immune response.

Additional tests showed that the Bifidobacterium did not leave the

intestine. They appeared to trigger the immune response by interacting with roaming dendritic cells. These scavenger cells detect and process potential threats and present them to the T cells. The researchers suspect that Bifidobacterium colonize a compartment in the intestines. This enables them to interact with the cells that interact with dendritic cells, which activate tumor-killing T cells.

There may be other bacteria that also contribute to this process, the researchers note, either positively or negatively. They are investigating other bacteria that could influence other immune therapies, such at the CTLA-4 pathway, exploited by ipilimumab.

A second study—from the Institut Gustave Roussy in Paris, published in the same issue of *Science*—found that antibiotics could disrupt the antitumor effects of ipilimumab. Replenishing lost microbes in germ-free and antibiotic-treated mice restored the drug's anti-cancer effects.

More information: "Commensal Bifidobacterium promotes anti-tumor immunity and facilitates anti-PD-L1 efficacy," by A.Sivan et al. *Science*, www.sciencemag.org/lookup/doi/ … 1126/science.aac4255

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