Response to Cancer Immunotherapy May Depend on Gut Bacteria

Summary includes updated data not in the abstract
For immediate release
February 21, 2017

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Expert Perspective:
“Immunotherapy is rapidly improving the lives of people with cancer, but it doesn’t work for many patients, and we still don’t know why,” said ASCO Expert Lynn Schuchter, MD, FASCO. “These results open the door for new approaches to boosting patients’ responses to PD-1 drugs, potentially by tinkering with the composition of gut bacteria.”

ALEXANDRIA, Va. – Researchers have found a link between microbes in the gut (the microbiome) and response to immunotherapy. In the study, the ability of patients with advanced melanoma to respond to PD-1 immune checkpoint inhibitors depended on the presence of a diverse microbiome as well as specific bacterial species. The study will be presented at the upcoming 2017 ASCO-SITC Clinical Immuno-Oncology Symposium in Orlando.

“Our findings are early, but if they are validated in larger cohorts across cancer types, they may have significant implications for cancer prognosis and treatment,” said study senior author Jennifer A. Wargo, MD, MMSc, associate professor of genomic medicine and surgical oncology at the University of Texas MD Anderson Cancer Center in Houston. “Meanwhile, we need concerted research efforts to better understand how the microbiome may influence immune responses, as well as an in depth view on how we can tweak the microbiome so that more patients can benefit from immunotherapy.”

In the human body, bacteria outnumber human cells by up to 10 to 1. The gut alone is home to 100 trillion bacteria, including more than a thousand different species. The composition of the microbiome can be very different from one person to the next, and the differences are believed to be influenced by factors such as exposure to microbes in early life and diet. In addition, there are distinct microbial communities in different parts of the body, such as the mouth, the gut and the
lungs.

“There has been a growing appreciation for the important role that the microbiome plays in immune defenses against cancer, with much of the work being done in mouse models. To our knowledge, this is one of the first studies to explore the association between the microbiome and immunotherapy response in people,” said lead study author Vancheswaran Gopalakrishnan, BDS, MPH, a PhD candidate at the University Of Texas School Of Public Health in Houston. Prior, preclinical studies in animal models demonstrated that changing the composition of the gut microbiome could enhance the efficacy of immune checkpoint inhibitors.

The Study
The researchers collected oral and gut (fecal) microbiome samples from 233 patients with advanced melanoma who were starting therapy. Among those patients, 93 received anti-PD-1 therapy. The diversity and composition of the oral and gut microbiome were assessed using a molecular technique called 16S rRNA sequencing, which identifies different bacteria according to their genetic signatures. The researchers also analyzed the composition and density of various immune cells in patient tumor samples.

Key Findings
In this study, significant differences were observed in the gut microbiome of responders versus non-responders to PD-1 inhibitors. Specifically, patients who responded to the PD-1 inhibitors had a more diverse gut microbiome than those who did not respond to this treatment though sample size was somewhat limited (total of 43 patients with available fecal samples, 30 who responded to therapy and 13 who did not). In addition, researchers found notable differences in the composition of the gut microbiome in responders versus non-responders. Patients who responded to treatment had an increased abundance of Clostridiales bacteria (specifically the Ruminococcaceae family) in the gut microbiome versus non-responders. On the other hand, patients who did not respond showed a greater abundance of Bacteroidales bacteria in comparison to responders.

Patients who benefited from PD-1 inhibitors also had a higher density of cancer-fighting immune cells known as CD8+ T cells in the tumor microenvironment than patients who did not benefit from the treatment. Researchers also found an association between CD8+ T cells in the tumor and a higher abundance of specific types of bacteria of the Ruminococcaceae family in the gut microbiome of the same patients.
The researchers also analyzed oral microbiome samples from all patients, but found no association between its diversity or composition and response to therapy. Dr. Wargo noted that it is still quite possible that the oral microbiome may play a role in immune response to other certain cancers, including lung and head and neck, though this needs to be carefully studied.

**Next Steps**

The research team is aiming to better understand the biological mechanisms through which the gut microbiome enhances systemic and anti-tumor immune responses. This work includes pre-clinical studies involving fecal transplant from human patients into germ-free mice, as well as other studies.

The authors are also designing clinical trials to test the hypothesis that modulation of the gut microbiome may enhance responses to immune checkpoint inhibitors. In collaboration with the Parker Institute for Cancer Immunotherapy, the first such trial is expected to launch later this year.

At the same time, future studies will explore the best way to tweak the microbiome composition. Besides fecal transplant, other strategies may involve use of antibiotics to selectively deplete certain bacteria or pre- or probiotic supplements to enhance certain bacteria into the gut.

**Research Funding**

This study was supported by the Moon Shot program at MD Anderson Cancer Center, the Melanoma Research Alliance and the Parker Institute for Cancer Immunotherapy.

[View the full abstract.](#)

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- Understanding Immunotherapy
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Established in 1984, the Society for Immunotherapy of Cancer (SITC) is the world’s leading non-profit organization of medical professionals dedicated to improving cancer patient outcomes by advancing the development, science and application of cancer immunotherapy and tumor immunology. SITC is comprised of influential basic and translational scientists, practitioners, healthcare professionals, government leaders and industry professionals from around the globe. Through educational initiatives that foster scientific exchange and collaboration among leaders in the field, SITC aims to one day make the word "cure" a reality for cancer patients everywhere.

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