Studies reveal new insights into gut microbiome impact on immunotherapy response in multiple cancers

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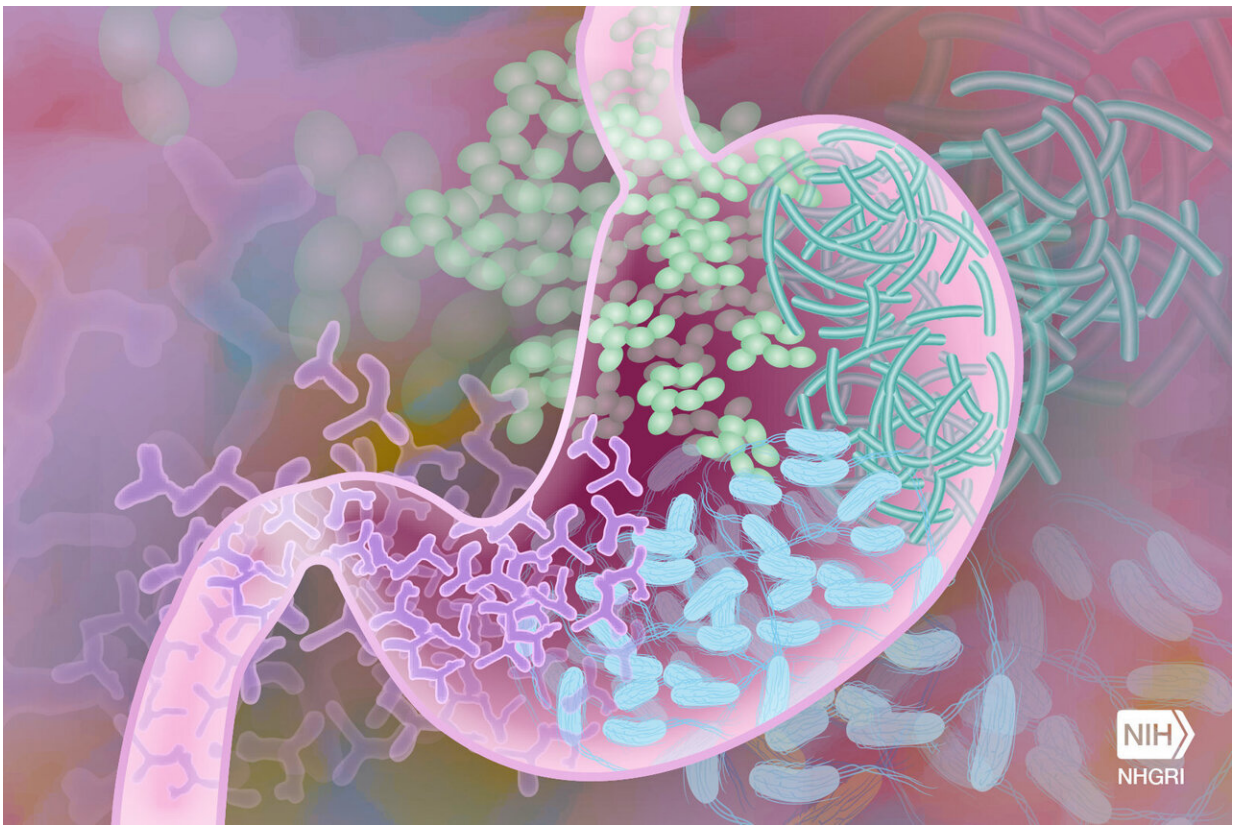

Illustration of bacteria in the human gut. Credit: Darryl Leja, National Human Genome Research Institute, National Institutes of Health

Two studies led by The University of Texas MD Anderson Cancer

Center that shed new light on the potential of the gut microbiome as a targetable biomarker to improve responses to immunotherapy were presented today at the 2022 American Society for Clinical Oncology (ASCO) Annual Meeting.

The findings include the first report of gut microbiome associations with immunotherapy response in newly diagnosed glioblastoma patients and a study that identified a link between gut microbiome signatures, immune cells in the tumor microenvironment and immune checkpoint blockade response in melanoma, non-small cell lung cancer (NSCLC) and sarcoma.

Gut microbiome signatures associated with immunotherapy response in glioblastoma (Abstract 2006)

Immunotherapy has had limited success so far against glioblastoma, the most common and aggressive form of brain cancer. A new study demonstrated that distinct gut microbiome signatures were present in patients with longer versus shorter survival following treatment with immune checkpoint inhibitors.

A Phase I/II clinical trial (NCT 03174197) investigating atezolizumab (anti-PD-L1) in combination with temozolomide and radiation therapy in newly diagnosed glioblastoma patients previously reported modest activity, with a median overall survival (OS) of 18 months and median progression-free survival of 10.6 months. The trial was designed with correlative studies to better understand the mechanisms underlying resistance to immune checkpoint inhibitor therapy, including stool collection to analyze the gut microbiome, a novel approach for glioblastoma.

"Although the addition of atezolizumab to standard-of-care radiation and chemotherapy did not improve the survival of patients with newly diagnosed glioblastoma, the correlative studies have given us insights into which patients might respond better than expected to immune checkpoint inhibitor therapy," said lead author and principal investigator Shiao-Pei Weathers, M.D., associate professor of Neuro-Oncology. "The challenge with immune checkpoint inhibitor therapy in glioblastoma is that there are select patients who do respond, and we need to better understand what characterizes these patients so we can tailor our treatment strategies."

The study included 45 stool samples collected from patients on the study before (26 samples) and after (19 samples) treatment. The researchers analyzed the gut microbiome composition and classified the results by OS, finding distinct differences between the baseline (pre-treatment) microbiomes of patients with shorter survival versus longer survival.

The clinical trial enrollment population was representative of glioblastoma incidence: 68% men, 87% non-Hispanic white and a median age of 57.8. Results from whole exosome and RNA sequencing on tumor tissue samples aligned with known genomic features of glioblastoma, including EGFR mutations associated with lower OS and IDH1 mutations associated with higher OS.

"We found distinct bacteria enriched in patients with long versus short survival, which is novel enough to warrant further investigation into this observation from a small sample size," Weathers said. "I think these findings may help increase excitement in immune checkpoint inhibitor therapy because it shows we still have a lot to learn about the gut microbiome and its potential role in response to immune checkpoint inhibitor therapy in glioblastoma."

As a result of this study, many clinical trials for glioblastoma at MD

Anderson now routinely include stool sample collection to enable correlative gut microbiome studies.

Gut microbiome associated with increased immune cell infiltration in the tumor microenvironment and response to immunotherapy across cancer types (Abstract 2511)

Recent research led by MD Anderson identified associations between neoadjuvant immune checkpoint blockade responses and B cells and tertiary lymphoid structures (TLS) in the tumor microenvironment. In this study, researchers built upon the previous work, finding further unifying evidence for these novel biomarkers of response and identifying a relationship between gut microbes, B cells and TLS across three cancer types: melanoma, NSCLC and sarcoma.

"If these findings are confirmed, we're hopeful that we could target cells in the tumor microenvironment through microbiome-directed therapies to increase B-cells and tertiary lymphoid structures in tumors and to enhance responses to immune checkpoint blockade," said lead author Elise Nassif, M.D., postdoctoral fellow of Surgical Oncology. Nassif received the GlaxoSmithKline Oncology Endowed Merit Award from the Conquer Cancer Foundation for the abstract.

The research team pulled data from three randomized Phase II neoadjuvant immune checkpoint blockade clinical trials led by MD Anderson and designed with similar protocols for specimen collection and timing: NCT02519322 (melanoma; 23 patients), NCT03158129 (NSCLC; 33 patients) and NCT02301039 (sarcoma; 17 patients). A total of 22 patients' cancers responded to treatment, based on the major pathological response criteria.

When team members analyzed the gut microbiome signatures and transcriptome data, they found that high pre-treatment levels of Ruminococcus were associated with response across cancer types. High levels of B cell infiltration and TLS formation at surgery (after immunotherapy) also were associated with response across cancer types.

Longitudinal data showed that B cells and TLS increased over the course of immunotherapy treatment in responders, but not in non-responders, and that this increase correlated with a gut microbiome signature that included high levels of Ruminococcus at baseline. B cells and TLS did not change in patients with low levels of Ruminococcus before treatment.

"The ideal should be to learn something from every patient, particularly for rare diseases," said senior author Christina Roland, M.D., associate professor of Surgical Oncology. "This study shows that we can really learn a lot from very small numbers of patients in well-designed clinical trials, even across multiple diseases, and that's critical to making big strides in cancer care."

More information: Abstract 2006: Shiao-Pei S. Weathers et al, Baseline tumor genomic and gut microbiota association with clinical outcomes in newly diagnosed glioblastoma (GBM) treated with atezolizumab in combination with temozolomide (TMZ) and radiation (2022)

Abstract 2511: Elise F Nassif, Identifying gut microbial signatures associated with B cells and tertiary lymphoid structures (TLS) in the tumor microenvironment (TME) in response to immune checkpoint blockade (ICB) (2022)

Provided by University of Texas MD Anderson Cancer Center