The Role of the Gut Microbiome in Breast Cancer Progression

BY WARREN FROELICH

Gut bacteria may help identify metastatic breast cancer patients who will respond positively to specific systemic cancer treatments, according to early findings by researchers from the City of Hope National Medical Center. The study, presented during the American Association for Cancer Research (AACR) Annual Meeting held April 10-15, 2021, provides growing evidence that the gut microbiome plays a role in the growth and progression of breast cancer and the response of metastatic breast cancer patients to cancer therapy (Abstract 336).

“Gut microbiota have emerged as a novel target to enhance the efficacy and reduce the toxicity and adverse effects of cancer therapy,” said Yuan Yuan, MD, PhD, Associate Professor in the City of Hope’s Department of Medical Oncology and Therapeutics Research and the study’s senior author.

Gut microbiota is composed of more than 100,000 billion bacteria and other microbes, including archaea, viruses, and a variety of eukaryotic organisms that reside in and on our bodies. Among other things, these micro-organisms contribute to the body’s metabolic functions, protect against pathogens, educate the immune system, and directly or indirectly play a key role in many of the body’s physiological functions.

Emerging studies also are demonstrating the potential of gut microbiota to predict treatment response in several tumor types, adding to a growing toolbox that personalizes treatment for cancer patients. Such knowledge not only could help predict patients who might benefit from specific types of cancer treatment, it also could reduce common adverse and toxic side effects triggered by some cancer therapies.

For example, a clinical study published in the June 2017 issue of Annals of Oncology suggested that gut microbiota could help identify patients who would respond favorably to ipilimumab—an immunotherapy targeting CTLA-4—to treat melanoma (https://doi.org/10.1093/annonc/mdx108). Likewise, other early studies have found that specific bacteria may be used to predict response for patients with colorectal cancer to chemotherapeutic drugs including 5-FU (Int J Colorectal Dis 2017; doi: 10.1007/s00384-017-2819-3).

In an interview, Yuan said it’s not clear why any specific bacterium promotes the efficacy of cancer treatment. However, she added these microbes generally work through several key mechanisms: immunomodulation, metabolism, enzymatic degradation, and reduction of diversity.

Asked how she would advise clinicians or patients about practices that might modify the gut microbiome before or during treatment, she said more studies were needed before issuing any clinical recommendations. “Results from this study are not ready to change clinical practice,” Yuan said. “We need a lot more study to verify results prior to use in patients (which will be a next step).”

In all, some 47 stool samples from 11 patients with stage IV metastatic breast cancer were collected at baseline and during treatment. Then, using a novel machine learning algorithm, Yuan and colleagues performed a metagenomic sequence analysis of gut microbiome that correlates with treatment response, particularly with immunotherapy and the targeted combination.

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Results per RECIST 1.1 (response evaluation criteria in solid tumors) were grouped into responders (complete or partial response) and non-responders (stable disease or progressive disease). Kruskal-Wallis tests were used to assess the differences of the most important microbiota relative abundance generated from the machine learning model between responders and non-responders.

For predictive modeling, the validation area under the ROC curve (AUROC) and area under the precision-recall curve (AUPRC) were 0.71 and 0.83, respectively.

Among the top five features from the model, patients with a larger relative abundance of Gemmiger formicilis had an increasing probability of responding to therapy (p<0.05 uncorrected). Interestingly, this same bacterium was reported to be higher in patients at baseline who experienced long-term benefit following treatment for colorectal cancer, Yuan said. Conversely, an increase in Bacteroides vulgatus showed a reduced probability of responding to therapy (p<0.05 uncorrected) in their study of breast cancer patients.

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Study Details

To study the association between gut microbiota and response to cancer therapy among metastatic breast cancer patients, the City of Hope researchers collected and analyzed stool samples from hormone-receptor positive (HR+) postmenopausal women participating in an ongoing Phase I trial designed to test the safety and efficacy of a drug combination that includes pembrolizumab, a CDK4/6 checkpoint inhibitor; palbociclib, a frontline CDK4/6 targeted therapy for HR+ metastatic breast cancer; and letrozole, an anti-hormonal agent designed to lower estrogen production.

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