The Rising Role of the Microbiome in Cancer

BY VERONICA HACKETHAL

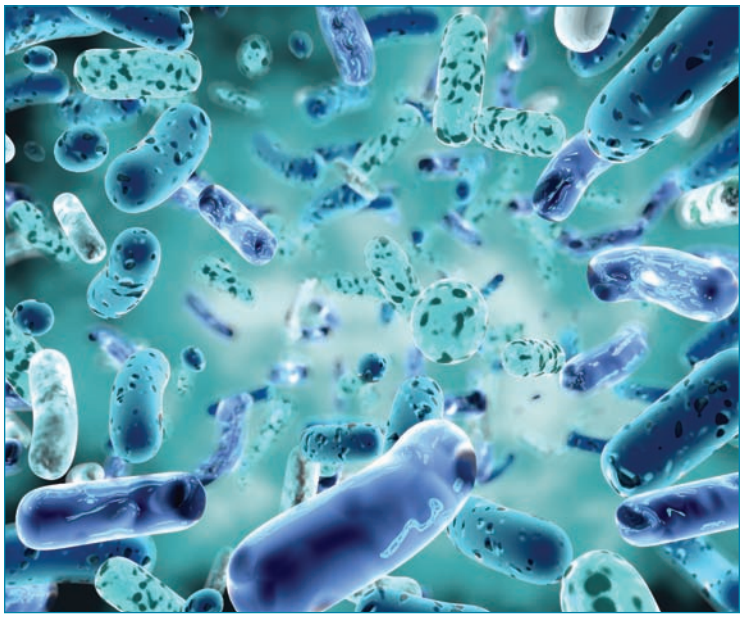
Humans harbor about as many microbes in and on their bodies as they have cells in their bodies: about 39 trillion (*PLoS Biol* 2016;14(8):e1002533). Most of these microbes reside in the gut and make up the gut microbiome, a diverse ecosystem of over 1,000 different species. The constituents and relative abundance of microbes in the gut microbiome vary widely between people, but four different phyla generally predominate in healthy individuals: *Firmicutes*, *Bacteroidetes*, *Proteobacteria*, *Actinobacteria*, and *Fusobacteria*.

The healthy balance of gut microbes can be offset by any number of things, but infections and medications are among the primary culprits. Scientists are now beginning to understand how the gut microbiome can contribute to disease, including cancer.

Microbiome in Cancer Development

Roughly 15-20 percent of human cancers may be attributable to microbial infection (*Lancet Oncol* 2012;13(6):607-615). For example, infection with *H. pylori*, hepatitis C virus, and human papillomavirus are risk factors for the development of stomach, liver and cervical cancer, respectively.

Gut commensals play an important part in human metabolism and immune function, and may also play a role in the development and progression of cancer (*CA Cancer J Clin* 2017;67(4):326-344). Possible mechanisms for their role in oncogenesis include generation of chronic inflammation and DNA damage, enhancement of cancer cell proliferation, and helping cancer cells evade



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immune detection. Microbes may also change normal adhesion between cancer cells and contribute to metastasis (*Curr Nutr Rep* 2019;8(1):42-51).

Imbalances in the gut microbiome, or dysbiosis, can cause decreased microbial diversity in favor of disease-promoting microbes. Examples of gut microbes associated with increased cancer risk include the following (*Curr Nutr Rep* 2019;8(1):42-51):

- *Salmonella enterica*: DNA damage and production of secondary bile acids that promote inflammation and tumor development;
- *Escherichia coli*: DNA damage and production of hydrogen sulfide, which may decrease mucous production and break down of the intestinal barrier; and
- *Fusobacterium nucleatum*: production of reactive oxygen species, reactive nitrogen species, and lipopolysaccharide, which causes inflammation and leaky junctions.

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Microbiome in Cancer Prevention

Not everyone who harbors harmful gut microbes develops cancer. That may depend on a complex interplay of other factors such as genetics, lifestyle (diet, exercise, smoking, alcohol consumption), and environmental exposure to toxins or other pollutants.

Among these factors, the impact of diet on the gut microbiome is perhaps the best understood. Obesity and calorie-rich diets high in protein and fat have been linked to increased production of potentially carcinogenic compounds. These include branched chain fatty acids, secondary bile acids, and N-nitroso compounds. Diets rich in fiber and plant compounds such as polyphenols, flavonoids, and glucosinolates (sulfur-containing compounds found in foods like broccoli and kale) have been linked to decreased cancer risk.

Gut commensals associated with cancer prevention include short-chain fatty acid (SCFA) producing bacteria such as *bifidobacterium longum*. SCFAs include acetate, propionate, and butyrate, and result from bacterial fermentation of complex carbohydrates and dietary fiber in the gut. These compounds, in turn, may help maintain intestinal tight junctions and nourish colon cells. Other beneficial bacteria include *lactobacillus acidophilus*, which may improve DNA maintenance, and *saccharomyces boulardii*, which may reduce DNA damage, reduce inflammation, and inhibit tumor growth (*Curr Nutr Rep* 2019;8(1):42-51).

Microbiome in Cancer Therapy

Microbes have long been used to treat cancer. For over a century, *mycobacterium bovis* has been used to treat bladder cancer, and other microbial products have been used for immune activation, induction of apoptosis, and inhibition of vasculogenesis (*Curr Nutr Rep* 2019;8(1):42-51).

Scientists are now building on that history and trying to harness the microbiome to improve the effectiveness of cancer therapy. A growing body of evidence now points to a role for using the microbiome to improve immunotherapy, particularly checkpoint inhibitor therapy targeting the CTLA-4 and PD-1 pathways (*J Immunother Cancer* 2019;7(1):108).

"The current working model is that there are likely certain bacteria that augment anti-tumor immunity and immunotherapy efficacy, yet other bacteria that interfere with these processes," Thomas Gajewski, MD, PhD, told *Oncology Times*. Gajewski is the AbbVie Foundation Professor of Cancer Immunotherapy at the University of Chicago, and senior author of a recent review article about the role of the microbiome in cancer immunotherapy (*J Immunother Cancer* 2019;7(1):108).

"Microbiome sequencing has been performed in cancer patients receiving checkpoint blockade immunotherapy, [and] bacterial sequences have been identified that are over-represented in responding patients. In addition, other bacterial sequences were enriched in non-responding patients," he said.

Observations such as these may help explain why response to checkpoint inhibitors varies greatly between patients. They may also

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provide some answers for variations in treatment-related toxicity, such as gastrointestinal and liver toxicity related to checkpoint inhibitor therapy. For example, some evidence suggests that a gut microbiome enriched with *Bacteroidetes* bacteria may protect against immune-mediated colitis associated with anti-CTLA-4 therapy (*Nat Commun* 2016 Feb 2;7:10391). Others have found that having an abundance of "good" bacteria in the gut microbiome was associated with better response to PD-1 blockade (*Science* 2017:eaan4236).

Future Applications

Scientists have proposed a number of potential applications for the microbiome in cancer therapy.

"Analysis of the gut microbiota could represent a useful predictive biomarker for immunotherapy efficacy," Gajewski noted.

DNA sequencing of fecal bacteria before therapy could be used alongside other biomarkers such as T-cell infiltration and tumor mutation burden to identify patients most likely to respond to therapy.

Gut bacteria could also be manipulated or altered to improve immunotherapy efficacy or decrease treatment-related side effects. One method could be fecal transplant from healthy donors, which is already being tested in early-phase clinical trials. Other methods include dietary interventions to encourage expansion of beneficial bacteria, administration of probiotics with beneficial properties, or administration of bacterial metabolites that modulate the immune system. Bacteriophages could also be used to kill off detrimental bacteria, or bacteria could be genetically engineered to produce a beneficial metabolite (*Curr Nutr Rep* 2019;8(1):42-51).

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>
> *—Thomas Gajewski, MD, PhD, AbbVie Foundation Professor of Cancer Immunotherapy at the University of Chicago*

However, Gakewski warns that these methods remain investigational and have no proven efficacy. Fecal transplant, in particular, could transmit pathogenic or multi-drug resistant organisms and may carry serious risks including death. For these reasons, clinical trial protocols are being adjusted to select fecal transplant donors more carefully.

Likewise, over-the-counter probiotics may be ineffective and could prove harmful. Early data suggests that some patients who take over-the-counter probiotics may be less likely to respond to anti-PD-1 therapies.

"One possible explanation is that if the bacteria in the probiotic are functionally irrelevant, they may displace the truly important bacteria from their niche in the gut," Gajewski said. "Therefore, our general recommendation is to avoid probiotics and to ensure a balanced diet that includes fresh fruits and vegetables, dietary fiber, and low-fat content."

He also advised judicious use of antibiotics. When used with immunotherapy, antiobiotics have been associated with shorter progression-free survival and shorter overall survival (*CA Cancer J Clin* 2017;67(4):326-344).

"Avoid antibacterial antibiotics unless they are absolutely necessary, as they may kill off potentially favorable commensal bacteria in the gut," he stressed. OT

Veronica Hackethal is a contributing writer.

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Learning Objectives for This Month's Activity:

After participating in this activity, readers should be better able to: 1. Analyze the function of the gut microbiome in the development or prevention of cancer. 2. Identify the role of the microbiome in cancer therapy.

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