

Microbiome, a new dimension in cancer research

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Recent reports on microbiome leading to or in association with cancer have surfaced in the medical science field. The results may impact clinical management as new concepts may provide a glimpse of a new world for cancer diagnosis, therapy and prevention. There will be profound implications for the discipline of medicine and oncology and for how laboratory diagnosticians relate to medicine as a whole. This editorial will provide a succinct, but challenging, analysis from a major article on the subject of cancer and microbiome, and how we anticipate the field of medical oncology will change during the next 5 to 10 years. In the *Science* publication of April 2015, Garrett highlights several mechanisms through which microbes and microbiota contribute to the development of cancer, whether by enhancing or diminishing a host's risk. The mechanisms fall into three categories: (I) modifying the balance of host cell proliferation and death; (II) piloting the function of the immune system; and (III) affecting the breakdown of host-generated factors, ingested food staples, and pharmaceuticals (1).

The influence of the host's microbiota on cancer susceptibility has been widely studied recently. Garrett eloquently strengthened the evidence that microbes and microbiota contribute to the development and progression of cancer, and the host's response to therapy (1). Of note, with respect to the millions of microbes living on earth, only ten are designated by the International Agency for Cancer Research (IACR) as carcinogenic to humans. However, there is speculation in regards to the implication of other microbes in carcinogenesis in mouse models and possibly humans (2,3).

There is a body of evidence that several bacteria can influence cancer risk via interfering with the β -catenin

signaling (4). For example, oncogenic type 1 strains of *Helicobacter pylori* express the protein CagA, which abnormally modulates β -catenin to drive gastric cancer. *Fusobacterium nucleatum* that has been implicated in colorectal adenomas and adenocarcinomas through the FadA also promotes the activation of β -catenin. Additionally, enterotoxigenic *Bacteroides fragilis* that is augmented in some human colorectal cancers and *Salmonella typhi* strains that have been associated with hepatobiliary cancers, promote activation of the β -catenin signaling via Btf and AvrA, respectively (1,5-7).

Carcinogenesis may result from the combination of persistent barrier breach along with a failure to restore homeostasis. Mucosal surfaces are susceptible to this barrier breach by way of constant environmental insults and a lack of homeostasis, altering host-microbial symbiosis. As a result, microbiota may alter the life cycle of a host cell, interrupt the function of the immune system, and impact the host metabolism (1).

Bacteria can damage the host DNA directly by genotoxins and indirectly by bacterium-induced/host-produced inflammatory mediators. For example, colibactin, a polyketide-peptide genotoxin encoded by pks island in *Escherichia coli* causes DNA damage via crosslinking duplex DNA. Although not proven in humans, colibactin-expressing *E. coli* has been found to enhance intestinal tumorigenesis in mice and has garnered interest in the role it plays in colorectal carcinogenesis. Conversely, *E. coli* and *Salmonella spp.* can utilize reactive oxygen and nitrogen species produced in inflammation as nutrients to modulate the chronic inflammatory reactions as a means to enhance cancer growth and spread (7,8).

To advance our understanding of the role of microbiota

in tumorigenesis, it is essential to comprehend both the beneficial and harmful effects of microbial metabolites. An illustration of the beneficial metabolites is short chain fat acids such as acetic, propionic, and butyric acids, produced by the intestinal fermentation of dietary fiber by members of the colonic microbiota (9). These fatty-acids employ their anti-inflammatory effects on myeloid cells and colonic regulatory T cells, reducing the cancer risk (9). The effects of short chain fatty acids are conducted by triggering a family of the cellular receptors, e.g., Niacr1/Gpr109a, Gpr43, Gpr41, or Olfr78. For instance, Gpr109a, expressed by both intestinal myeloid and epithelial cells, is a receptor for niacin and butyrate that performs a vital function in facilitating the effects of dietary fiber on the microbiota of the colon. Activation of Gpr109a by butyrate results in anti-inflammatory host feedbacks in myeloid cells that lead to regulatory T cell generation, and loss of Gpr109a predisposes to colitis-associated colorectal cancer (1,9). One of the offenders is high saturated fat intake that heightens cancer risk for reasons not yet fully understood. One theory views obesity as an inflammatory condition in line with the conventional wisdom that inflammation enhances cancer risk (9). A binding trio that comprises obesity, the microbiota and inflammation powers carcinogenesis; a concept that is corroborated by recently published data (1,10). Another relevant theory that has been investigated by numerous studies links a high fat diet to cancer risk through the bile acid pathway. Succinctly, high fat food increases bile acid secretion into the digestive tract. Secondary bile acids, converted only by gut bacteria, can accrue to high levels in the gut and may contribute to the pathogenesis of cancer of the laryngopharyngeal tract, esophagus, stomach, pancreas, the small intestine and the colon (11).

With the widening acceptance of gut microbiota function in drug metabolism, influencing toxicity and efficacy, there is interest in the microbiota's modulation of chemotherapy toxicity and efficacy. Conceptually, the cause and effect relationship between gut microbiota and medications has been established. Medications (i.e., irinotecan, oxaliplatin, and cyclophosphamide) might have an impact in the gut microbiota which can also influence the effectiveness of chemotherapy (1,12). Henceforward, studies defining the response of gut microbiota to chemotherapy and microbiome scrutiny in patients with and at risk for cancer will be judicious to comprehend the utility of microbiota as an adjuvant therapy that augments effectiveness or mitigates toxicity of chemotherapies.

Another therapeutic modality that has gained attention

in the combat of cancer is immunotherapy in the form of cytokine and vaccine therapy. In light of the intermingled nature of the microbiota and the immune system, it is conceivable that the microbiota influence a host's responsiveness to immunotherapy. In truth, tumors such as melanoma, bladder, renal, and lung cancer have shown response to immunotherapy (1,13). Nonetheless, the same response has not been observed in colon cancer, intensifying curiosity in how the microbiota manipulate immunotherapy's efficacy. It is irrefutable that bacteria may trigger the immune system to attack and destroy cancer cells. The *Bacillus Calmette-Guerin* (BCG), a perfect embodiment of this theory, is often administered in the form of a live vaccine used for the treatment of urothelial carcinoma that is not invasive into the muscle. The bacteria administered into the bladder by way of the BCG vaccine provokes an inflammatory reaction that ignites an antitumor immune response (1,14).

Microbiota studies in cancer remain at an early stage. In recent years, breathtaking advances in understanding the role of microbiota in cancer susceptibility have occurred at many levels. The pace of change is dizzying, both in numbers of studies and in the complexity of results. Given that many of the studies were performed in animal models, attention should be paid to their relevance to human cancers. The true pathophysiologic mechanisms related to microbes and innate and adaptive immune responses to tumors, as well as the repercussions on cancer progression and whether tumors subsequently become resistant or susceptible to different anticancer therapeutic regimens still are under investigation. It is conceivable to envision that within the next decade or so the identification of key contributors to microbiota-driven carcinogenesis will be unraveled facilitating tailored cancer therapeutic and preventive approaches.

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Footnote

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