

## The oncobiome – the next frontier?

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Cancer is a major health problem, with about 10 million deaths by 2020 worldwide, according to WHO (1). Currently, in terms of microbiota, studies have shown that it intervenes in the body in multiple processes. So does the question arise whether this microbiota can also involve in the cancer’s etiology?

Can the microbiota intervene in the mechanisms that generate cancer, or is its role in favoring or not its evolution? The answer to this question was the main topic, how can we introduce a series of information about the microbiota in a potential cancer screening? Recent studies have shown microbes’ direct and indirect involvement in oncogenesis (2,3), immunotherapeutic modulation, and pre-and postbiotic effects (4).

The intervention could require a change in the therapeutic and/or prognostic regimens of various forms of cancer. Compared to the well-known role of viruses in oncogenesis, that of microbes is less known. The first evidence was related to the relationship between *Helicobacter pylori* and non-cardiac gastric carcinoma. A possible mechanism would be the proinflammatory effect of oxidative stress with DNA alteration that can lead to carcinoma (5). However, the eradication of *H. pylori* is associated with a slight decrease in the incidence of gastric cancer (6).

The host-microbe relationship regarding carcinogenesis is best defined by colorectal cancer. Another question would be about when this investigation should be considered? In CRC, screening begins at age 50 for medium-risk patients by testing stool with

increased stool sensitivity. Zeller et al. used metagenomic sequencing to use a series of stool markers to identify patients with CRC (7). Regarding CRC detection, the sensitivity and specificity of taxonomic markers were approximately similar to fecal occult blood testing; the combined use statistically significantly increased the detection rate. The fecal immunochemical test (FIT) is the best example of a screening element for CRC globally (8). The role in CRC carcinogenesis of *Fusobacterium nucleatum* is predominantly immunomodulatory such as the proliferation of myeloid-derived suppressor cells and inhibitory receptors of natural killer cells, and intervention in the intracellular metabolism of bacteria (9). Furthermore, the proposed screening should be prophylactic and not based on early detection of signs of malignancy.

Technology on detecting APC or KRAS mutant genes in tumor cells did not observe their increased sensitivity and specificity (10).

The relationship between the oncogenesis process and the microbiota can be based on the diet regarding the active mechanism of action to prevent malignant disease. Studies have not shown that dietary changes can directly influence the carcinogenetic process, but only the microbiota. The topographic highlighting of several areas regarding the microbiome, intestinal, vaginal, oral, pulmonary, and renal, can reveal the possible role in microbiome-related oncological diseases (figure 1).

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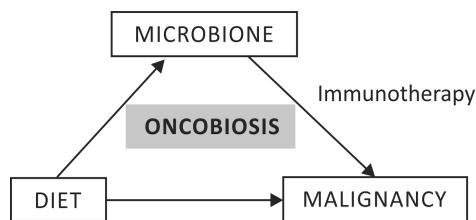
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**FIGURE 1.** The relationship between diet – microbiome – malignancy

Alterations of the intestinal mucosa accompany intestinal dysbiosis, a marked decrease in antitumor substances (short-chain fatty acids), decreased local immunity, a chronic inflammatory process, with a severe local metabolic imbalance. These mechanisms promote both intestinal carcinogenesis and the female genital tract (11). Oncobiosis found in ovarian cancer is related to the multiplication of gram-negative bacterial colonies, an important role being played by vaginal infections with *Neisseria gonorrhoeae* or *Chlamydia trachomatis*. In addition, peritoneal colonization may have a role in its metastasis (12,13). In contrast, in breast cancer, the mechanisms of action are different by the action of bacterial metabolisms, by hormone-like autocrine/paracrine mechanisms. The roles of the microbiome in breast cancer focus on identifying biomarkers for early detection and screening of patients and increased survival (14).

The identification of microbes within the microbiome can be important in immunotherapy through the inhibitory action in the cell cycle or the secretion of some metabolites by coupling them with toll-like receptors (TLRS) or antigen-presenting cells (APCs) (15,16). The host immune system recognizes the mo-

lecular models associated with microorganisms (MAMP) in the microbial structure.

The antitumor activity of chemotherapy is modulated by the maturation of helper T cells by the local microbiota. Thus, probiotic immunotherapy is a part of oncobiome.

The relationship between dysbiosis and cancer has led to the idea that microbial genomics could identify biomarkers in different types of cancer (3).

The prophylactic anticancer mode of action of the microbiota can be achieved through detoxification mechanisms or through various metabolites with the antioxidant role (17). Combining microbiome modulation with conventional immunotherapy may be a step forward in personalized cancer therapy (18).

Restoring the functionality of the microbiome either by microbiome transplantation or by administration of pre/probiotics or by genetically modified microbiota will cause a marked decrease in proliferative, inflammatory, and apoptotic phenomena (19).

Future research will focus on deciphering the microbiome-host mechanisms and their influence in the prevention, diagnosis, and therapy of various oncological diseases. There is currently no direct evidence of involvement of the human microbiota related to cancer initiation and progression. Studies related to chemotherapy in various forms of cancer are currently being considered and the microbiota in terms of its metabolism and effectiveness. It is also not known if some forms of cancer are affected by the local microbiota but, in fact by the body's microbiome at all levels.

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## REFERENCES

1. WHO. Cancer. Available at: <https://www.who.int/news-room/fact-sheets/detail/cancer>.
2. Rajagopala SV, Vashee S, Oldfield LM, Suzuki Y, Venter JC, Telenti A, Nelson KE. The Human Microbiome and Cancer. *Cancer Prev Res (Phila)*. 2017 Apr;10(4):226-234.
3. Matson V, Chervin CS, Gajewski TF. Cancer and the Microbiome-Influence of the Commensal Microbiota on Cancer, Immune Responses, and Immunotherapy. *Gastroenterology*. 2021 Jan;160(2):600-613.
4. Choudhry H. The Microbiome and Its Implications in Cancer Immunotherapy. *Molecules*. 2021 Jan 3;26(1):206.
5. Shimizu T, Chiba T, Marusawa H. Helicobacter pylori-Mediated Genetic Instability and Gastric Carcinogenesis. *Curr Top Microbiol Immunol*. 2017;400:305-323.
6. Sukri A, Hanafiah A, Mohamad Zin N, Kosai NR. Epidemiology and role of Helicobacter pylori virulence factors in gastric cancer carcinogenesis. *APMIS*. 2020 Feb;128(2):150-161.
7. Zeller G, Tap J, Voigt AY, Sunagawa S, Kultima JR, Costea PI, et al. Potential of fecal microbiota for early-stage detection of colorectal cancer. *Mol Syst Biol*. 2014 Nov 28;10(11):766.
8. Tepus M, Yau TO. Non-Invasive Colorectal Cancer Screening: An Overview. *Gastrointest Tumors*. 2020 Jul;7(3):62-73.
9. Hashemi Goradel N, Heidarzadeh S, Jahangiri S, Farhood B, Mortezaee K, Khanlarkhani N, Negahdari B. Fusobacterium nucleatum and colorectal cancer: A mechanistic overview. *J Cell Physiol*. 2019 Mar;234(3):2337-2344.
10. Ng C, Li H, Wu WKK, Wong SH, Yu J. Genomics and metagenomics of colorectal cancer. *J Gastrointest Oncol*. 2019 Dec;10(6):1164-1170.
11. Borella F, Carosso AR, Cosma S, Preti M, Collemi G, Cassoni P, Bertero L, Benedetto C. Gut Microbiota and Gynecological Cancers: A Summary of Pathogenetic Mechanisms and Future Directions. *ACS Infect Dis*. 2021 May 14;7(5):987-1009.
12. Sipsos A, Ujlaki G, Mikó E, et al. The role of the microbiome in ovarian cancer: mechanistic insights into oncobiome and to bacterial metabolite signaling. *Mol Med*. 2021;27(1):33.

13. Banerjee S, Tian T, Wei Z, Shih N, Feldman MD, Alwine JC, Coukos G, Robertson ES. The ovarian cancer onco biome. *Oncotarget*. 2017 May 30;8(22):36225-36245.
14. Bodai BI, Nakata TE. Breast Cancer: Lifestyle, the Human Gut Microbiota/Microbiome, and Survivorship. *Perm J*. 2020;24:19.129.
15. Alexander JL, Wilson ID, Teare J, Marchesi JR, Nicholson JK, Kinross JM. Gut microbiota modulation of chemotherapy efficacy and toxicity. *Nat Rev Gastroenterol Hepatol*. 2017 Jun;14(6):356-365.
16. Peneş NO, Weber B, Păun SD. Role of genetic polymorphism in nutritional supplementation therapy in personalized medicine. *Rom J Morphol Embryol*. 2017;58(1):53-58.
17. Schwabe RF, Jobin C. The microbiome and cancer. *Nat Rev Cancer*. 2013 Nov;13(11):800-12.
18. Singh RP, Bashir H, Kumar R. Emerging role of microbiota in immunomodulation and cancer immunotherapy. *Semin Cancer Biol*. 2021 May;70:37-52.
19. Chilakapati SR, Ricciuti J, Zsiros E. Microbiome and cancer immunotherapy. *Curr Opin Biotechnol*. 2020 Oct;65:114-117.