Cancer and Metastasis Reviews (2022) 41:247–248
https://doi.org/10.1007/s10555-022-10035-5

EDITORIAL

# Microbes and cancer: disease drivers, passengers, biomarkers, or therapeutics?

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Published online: 4 May 2022


In the past 20 years, we have experienced a growing and innovative field investigating the vast human microbiota and its influence on health and disease pathogenesis. From this, we anticipate new prevention and therapeutic strategies for an increasing number of cancer types. In most cancers, microbiome research has flourished over the last 5–10 years. This is aptly illustrated in this issue of *Cancer and Metastasis Reviews* which contains important discussions of the findings and impact of microbiome research across colon, esophageal, pancreatic, and lung cancers, as well as melanoma, multiple myeloma, and hematopoietic malignancies. These papers discuss important cancer microbiome associations—local, systemic, and/or cancer-specific—and an early appreciation of mechanistic mediators focusing on immune responses, microbial metabolites, and/or the tumor microenvironment as well as responses to immunotherapy.

In some instances, the findings in the microbiome field have been nearly astonishing. One clear example is the extraordinary power of diet to quickly manipulate our gut microbiota and its function as illustrated in a human short-term diet switch experiment utilizing high-fiber/low-fat and low-fiber/high-fat diets [1]. In contrast, individual and strong regional gut microbiota differences limit developing clear healthy microbiota standards against which new data can be reliably compared [2]. Colon cancer is strongly associated with a disrupted microbiota but associating a specific microbiota context with risk for colon pre-neoplasia able to be implemented for colorectal cancer (CRC) prevention remains elusive [3]. The unexpected observation of a pancreatic microbiome with potential oral and/or fecal microbiome contributors presents the opportunity to provide a new entry point for understanding and manipulating this deadly cancer.

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What are some key variables that clinical and/or translational investigators must consider when taking on a cancer: microbiome project? First is the careful consideration of study design and assembly of clinical metadata. Currently, many, if not most studies, have been relatively small, cross-sectional, and/or lack adequate, if any, controls, including inconsistent reporting of clinical metadata. We have increasingly recognized the breadth of the exposome [4] with available data supporting that the gut microbiome is affected by numerous extrinsic (e.g., diet, medications) and intrinsic (e.g., somatic and epigenetic gene variability, fecal water content, immune responses, co-morbidities) host factors, which are details not routinely captured or analyzed in many microbiome studies. There is debate about what tool or how to accurately capture, for example, diet. Second is the broad range of technical components that hinder reliable microbiome sequencing (e.g., 16S rRNA, metagenomic, RNA) and analysis including sample collection, storage, DNA extraction, site-dependent sequencing differences, and analytical tools among others. Third is the need to "take the next step," namely, validating conclusions from computational studies using independent, orthogonal approaches such as biomarkers, biology, metabolome measurements, and/or animal models. Fourth, at this juncture, investigators need to consider and address how well animal models parallel human results, given the observations of Walter and colleagues [5], who pointed out the marked differences in the strength of conclusions derived from animal models vs human studies about the role of the microbiome in disease pathogenesis.

What approaches might help investigators achieve their goals to sample and analyze the microbiome to improve cancer prevention and/or therapeutic outcomes? A key first is expanding the investment in longitudinal studies in high-risk children and adults with hereditary cancer syndromes and/or those with pre-neoplasia or early-stage cancers where microbiome impacts from prior therapies should be lessened. Early data on microbiota: host gene impacts, including inflammatory bowel diseases that exhibit increased gut

cancer risk, and/or potential microbiome instability with serial antibiotic exposures [6] raise the question whether individual differences in microbiome assembly and/or recovery are important to the individual risk for onset and the course of cancer as well as other chronic diseases. Certainly, substantive data now suggest that antibiotic exposure early in immunotherapy hampers its efficacy [7], and the rising tide of early-onset CRC suggests that changing exposures in childhood may, in part, underpin this deadly trend. A second area to address is improving the requirements for and consistency of microbiome data reporting to enable cross-study comparisons to be more readily made. One recent suggestion to strengthen the presentation, assessment, and understanding of microbiome research across studies is for a 17-point "Microbiome Reporting Checklist" to be used (STORMS, Strengthening the Organization and Reporting of Microbiome Studies) [8], an approach akin to CONSORT (Consolidated Standards for Reporting Trials) guidelines for reporting of clinical trials. Third, given the early promise of data-driven, quality-controlled microbiome therapies such as the development of microbiota-directed complementary foods [9] or SER-109 as a possible therapy for recurrent *Clostridioides difficile* disease [10], we need an accelerated commitment to developing prospective, controlled human trials of microbiome-modifying products supported by in-depth cross-disciplinary science and likely re-imagined and better integrated training of our medical scientists.

Many directions with exceptional promise for microbiome science and cancer are emerging. We are at a threshold where the "race to publish" should be tempered by the desire to build better-designed and -analyzed studies, to enhance intra- and inter-discipline communication, and to validate results from both human and animal studies. These steps will hasten our ability to bring new, reliable microbiome-derived tools and therapies to yield our desired outcomes, cancer prevention, and life-extending, life-improving therapies that complement traditional cancer therapy approaches.

## References


1. O'Keefe, S. J., Li, J. V., Lahti, L., Ou, J., Carbonero, F., Mohammed, K., et al. (2015). Fat, fibre and cancer risk in African Americans and rural Africans. *Nature Communications, 28*(6), 6342. https://doi.org/10.1038/ncomms7342.
2. He, Y., Wu, W., Zheng, H. M., Li, P., McDonald, D., Sheng, H. F., et al. (2018). Regional variation limits applications of healthy gut microbiome reference ranges and disease models. *Nature Medicine, 24*(10), 1532–1535. https://doi.org/10.1038/s41591-018-0164-x Erratum in: Nat Med. 2018 Sep 24.
3. Thomas, A. M., Manghi, P., Asnicar, F., Pasolli, E., Armanini, F., Zolfo, M., et al. (2019). Metagenomic analysis of colorectal cancer datasets identifies cross-cohort microbial diagnostic signatures and a link with choline degradation. *Nature Medicine, 25*(4), 667–678. https://doi.org/10.1038/s41591-019-0405-7 Erratum in: Nat Med.
4. Vermeulen, R., Schymanski, E. L., Barabási, A. L., & Miller, G. W. (2020). The exposome and health: Where chemistry meets biology. *Science, 367*(6476), 392–396. https://doi.org/10.1126/science.aay3164.
5. Walter, J., Armet, A. M., Finlay, B. B., & Shanahan, F. (2020). Establishing or exaggerating causality for the gut microbiome: Lessons from human microbiota-associated rodents. *Cell, 180*(2), 221–232. https://doi.org/10.1016/j.cell.2019.12.025.
6. Dethlefsen, L., & Relman, D. A. (2011). Incomplete recovery and individualized responses of the human distal gut microbiota to repeated antibiotic perturbation. *Proceedings of the National Academy of Sciences of the United States of America, 108*(Suppl 1), 4554–61. https://doi.org/10.1073/pnas.1000087107.
7. Routy, B., Le Chatelier, E., Derosa, L., Duong, C. P. M., Alou, M. T., Daillère, R., Fluckiger, A., Messaoudene, M., Rauber, C., Roberti, M. P., Fidelle, M., Flament, C., Poirier-Colame, V., Opolon, P., Klein, C., Iribarren, K., Mondragón, L., Jacquelot, N., Qu, B., et al. (2018). Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors. *Science, 359*(6371), 91–97. https://doi.org/10.1126/science.aan3706
8. Mirzayi, C., Renson, A., Zohra, F., Elsafoury, S., Geistlinger, L., Kasselman, L. J., et al. (2021). Reporting guidelines for human microbiome research: The STORMS checklist. *Nature Medicine, 27*(11), 1885–1892. https://doi.org/10.1038/s41591-021-01552-x.
9. Chen, R. Y., Mostafa, I., Hibberd, M. C., Das, S., Mahfuz, M., Naila, N. N., et al. (2021). A microbiota-directed food intervention for undernourished children. *New England Journal of Medicine, 384*(16), 1517–1528. https://doi.org/10.1056/NEJMoa2023294.
10. Feuerstadt, P., Louie, T. J., Lashner, B., Wang, E. E. L., Diao, L., Bryant, J. A., et al. (2022). SER-109, an oral microbiome therapy for recurrent *Clostridioides difficile* infection. *New England Journal of Medicine, 386*(3), 220–229. https://doi.org/10.1056/NEJMoa2106516.