GUT MICROBIOTA

Microbes offer engineering strategies to combat cancer

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This commentary outlines our expanding opportunities to harness the gut microbiota for cancer prevention and remission. Ultimately, simple microbial strategies might impart immune balance throughout the body leading to sustained good health.


Studies have revealed that gut bacteria and immune cells exist with interactive networks that dictate good health and disease, including cancer, both within and beyond the gut. This emerging paradigm linking gut bacteria with extraintestinal cancer builds upon earlier work that tumour microenvironments interact with systemic immune and metabolic networks, and, more specifically, with microbial–immune networks. In this way, gut microbes influence cancer outcomes. The concept that a unified microbe–host holobiont (defined as the whole host organism plus resident microbiota) influences progression of cancer, and even cardiovascular disease and mental health, is both clinically relevant and captivating. Given that microbes generally outnumber host cells 10:1, it follows logically that crosstalk between the gut microbiota and host immunity is continuous and reciprocal throughout the host’s life. In fact, microbial–immune interactions constitute part of a vast gut–immune–brain signalling axis that continuously modulates IFNγ, CD4+ regulatory T (T<sub>REG</sub>) cells and host inflammatory tone. It remains to be determined how vast an effect microbial strategies will have on what are now intractable disease challenges. A new study by Vetizou et al. sheds light on this issue, revealing that the gut microbiota modulates patient responses to cancer immunotherapy.

Specifically, Vetizou et al. discovered that the antitumour effects of the cytotoxic T-lymphocyte protein 4 (CTLA‑4) blockade immunotherapy agent ipilimumab, an approved negative regulator of T-cell activation, rely in part upon resident gut bacteria. Using samples from patients undergoing immunotherapy for small cell lung carcinoma or malignant melanoma, combined with elegant germ-free and adoptive T-cell transfers in animal models, they showed that certain Bacteroides spp. are critical for host immunostimulatory responses and therapeutic success against the cancer target. Immunomodulatory effects of Bacteroides spp. were evidenced by induction of a type 1 T’ helper (T<sub>H1</sub>) response in lymph nodes draining the tumour site. In this setting, immune checkpoint blockade of CTLA‑4 led to host T<sub>H1</sub>-cell inflammatory responses that favoured certain symbiotic microbe populations contributing to therapeutic efficacy with fewer adverse effects. These results have profound implications not only for cancer immunotherapy, but also for novel strategies using microbiome engineering in cancer prevention and treatments separate from immunotherapy (FIG. 1).

The gut microbial dynamics documented by Vetizou et al. during immunotherapy also provide insight into complex microbe–immune feedback loops during host homeostasis. Although it is well established that microbial infections stimulate host T<sub>H1</sub> responses and IFNγ in order to extinguish a mucosal pathogen and stimulate tissue repair, excessive and/or chronic inflammation are detrimental to the host. Thus, an immune balance between pro-inflammatory and anti-inflammatory activities is the ultimate goal. The potential to creatively harness the microbe-driven immune balance hints at

Figure 1 | Microbe exposures stimulate the immune system against cancer. Whole organism physiology regulates neoplastic development, growth and invasion of extraintestinal cancers via gut bacterial interactions that modulate systemic inflammatory tone. Symbiotic gut microbe exposures stimulate a biased T<sub>H1</sub> and T<sub>REG</sub> cell response culminating in robust yet tightly-regulated immune responses to rapidly restore whole body homeostasis. These combined immune events inhibit cancer growth. Thus, neoplastic development and growth is framed in the context of the holobiont, including resident microbes or synthetic microbe cocktails, plus the host immune response, which we might engineer for personalized or public health goals. T<sub>REG</sub>, regulatory T cell; T<sub>H1</sub>, type 1 T helper cell.
great promise for cancer therapy. Prior evidence exists for host responses to microbes or microbial products3,6 stimulating CD4+ T-cell–mediated protection from tumour development6,9,10. However, the idealized quest for microbe-driven immune balance must consider how gut commensal bacteria, such as Helicobacter hepaticus1 or Bacteroides fragilis11, might contribute to cancer growth via upregulation of type 17 T helper cell pathways3,6,9, or, under other circumstances, inhibit cancer12. Constructively directing such host immune biases is a future challenge that requires further understanding of host and microbe genetics, other resident microbiomes, and timing of microbial exposures earlier in life9.

Beyond immunotherapy, dietary strategies using bacterial cocktails, such as with B. fragilis9, have appeal to stimulate beneficial antitumour immunity beyond checkpoint blockade. However, this ideal of simply supplementing patients with ‘good’ microbes or bacterial polysaccharides13,14 to induce CD4+ T-cell balance might actually require a more comprehensive strategy. Microbial communities, whether native or synthetic, are fluid and respond to environmental stimuli on daily timescales, according to host diet and other factors. Thus, coupling dietary fibres with microbial supplements could ultimately be more effective in hindering cancer progression. Surprisingly, studies in mouse models dissecting temporal dynamics of epithelial wound healing mimicking carcinogenesis showed that microbial symbionts, for example Lactobacillus reuteri, served to briefly stimulate inflammation for constructive wound repair and afterwards rapidly restore balance8. In that setting, oral supplementation with a single probiotic organism, L. reuteri, was sufficient to stimulate rapid tissue repair without concomitant immunotherapy.

Application of highly reductionist mouse models allows dissection of mechanisms simply not possible in human patients. Vetizou et al.3 used elegant transplants of microbiota and tissues into germ-free and specific pathogen-free animals to reveal that immunotherapy and host microbiome composition are quite interactive4. In this way, animal models peer into the exciting future of translational medicine. On the other hand, animal models could unveil substantial challenges ahead. For example, resident intestinal microbiota (and undoubtedly the corresponding immune systems) of mice might dramatically alter research outcomes and conclusions8. The dramatic differences between research results from laboratories using the same model system, but with different microorganisms, might help explain the divergence in treatment outcomes in human patients with cancer. Taken together, supplementing with a single microbe might be trivial or it might involve complex microbial interactions. Even with all of this, there’s reason for optimism. Probiotic bacteria have been consumed daily by civilizations worldwide for centuries with few unfortunate consequences.

... gut bacteria and immune networks that dictate good health and disease...

The notion that bacteria, such as those in fermented foods, are beneficial to an animal host has been fundamental in ancient societal practices, but has been slow to gain favour in recent decades. Modern management of microbial ‘enemies’ instead encourages widespread use of antibiotics and compulsive public hygiene practices. The concept of microbe-induced good health is most accepted in the hygiene hypothesis whereby early life exposures lead to a healthy, balanced immune system. The hygiene hypothesis postulates that too few microbial exposures early in life undermines the ability of the adult immune system to efficiently distinguish self from nonself, resulting in uncontrolled chronic inflammatory responses2. Individuals with dysregulated CD4+ T cells suffer life-threatening inflammatory responses1,3. This reality brings the microbe-immune dynamic (the holobiont) to the forefront of medicine, and perhaps cancer, not only in the here-and-now, but also for future generations.

An unanswered question is whether altering diet and microbes alone is sufficient for rescue from cancer. Restructuring the host immune system by targeting bacteria, without immune checkpoint blockade, is less invasive and more attractive owing to a reduced risk of IBD and other immune disturbances in animal models and patients5. Microbes might ultimately restore host immune balance and ablate cancer from the bottom up.

Recognizing the potential potency of microorganisms to boost immunotherapy raises hopes that engineering gut bacteria will deliver a constructive holobiont for sustained cancer remission. Microbiome engineering challenges appear unsurmountable and at the same time well within our grasp. Lessons learned from B. fragilis, H. hepaticus and L. reuteri indicate that even a single species of microbe can potentially transform the immune system and yield whole body health. Taken together, the work of Vetizou et al.8 and others helps usher in a new era of such microbe-driven holobiont engineering seeking freedom from cancer, as well as other systemic disorders of the cardiovascular system and mental health.

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The author declares no competing interests.