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Editorial

# Science in Focus: The Microbiome and Cancer Therapy

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## Introduction

In less than two decades since the term was coined, the human microbiome has become a key focus of research across a wide range of biomedical disciplines [1,2]. Knowledge that individual microbial constituents, such as *Helicobacter pylori*, can drive carcinogenesis predates this definition, but our understanding of the relationship between the human host and the trillions of bacteria that colonise our epithelial barrier surfaces continues to grow (for a primer on the microbiome, we draw the reader's attention to 'The vocabulary of microbiome research: a proposal' [3]). In this Science in Focus Editorial, we detail recent breakthroughs shedding light on the role of intestinal bacterial communities (the microbiota also consist of viruses, fungi, archaea and protozoa, which have received less attention to date) and how they shape mucosal and systemic immunity, and influence response to cancer treatments. We will discuss how the microbiota impact both positively and deleteriously on conventional chemotherapy, look at evidence that radiotherapy interacts with the microbiota and tackle the complex interplay between immunotherapy, the microbiota and the host immune system. Together these new insights raise the intriguing possibility of therapeutically exploiting this complex ecosystem to improve cancer outcomes.

## The Microbiota and Chemotherapy

To understand how the microbiota might influence aspects of chemotherapy treatment, we will first use the example of colorectal cancer (CRC). *Fusobacterium nucleatum,* an anaerobic bacterium usually resident in the oral cavity, is over-represented in the colons of patients with CRC. Cancers with high amounts of *F. nucleatum* are associated with a poor prognosis [4]. *Fusobacterium nucleatum* is enriched in recurrent CRCs relative to non-recurrent CRCs [5]. Moreover, by co-culturing the bacterium with CRC cells, *F. nucleatum*, in contrast to other constituents of the gut microbiota, reduced the apoptotic effects of 5-fluorouracil and oxaliplatin chemotherapy on HCT116 cell apoptosis. A plausible mechanism for this effect was shown through the modulation of the autophagy pathway via bacterial targeting of TLR4 and MYD88 signalling.

In contrast to the detrimental effects of *F. nucleatum*, evidence from mouse models suggests that a number of bacteria bestow anti-cancer qualities in the chemotherapy setting. Gram-positive bacteria including *Lactobacillus* and segmented filamentous bacteria stimulate the accumulation of TH17 and TH1 cell responses necessary for cyclophosphamide efficacy in mice inoculated with MCA205 tumours [6]. *Enterococcus hirae* and *Barnesiella intestinihominis* have been further implicated as players in cyclophosphamide treatment facilitation, the former by increasing the intra-tumoral CD8/Treg cell ratio, the latter by promoting the tumoral infiltration of interferon γ-producing γδ-T cells [7]. The microbiota can also facilitate the peri-tumoral production of inflammatory cytokines by myeloid cells in response to oxaliplatin treatment [8].

In addition to their impact on chemotherapy efficacy, the microbiota also influence drug toxicity (Figure 1). An archetypal example is irinotecan-induced diarrhoea, which can be dose limiting in many patients. The active metabolite of irinotecan, SN-38, is glucuronidated in the liver and is excreted via the gut, where it is released by bacterial beta-glucuronidase enzymes common to many species of bacteria resident in the colon, resulting in diarrhoea [9]. Gastrointestinal toxicity secondary to methotrexate and doxorubicin may also be facilitated by the microbiota [10,11].

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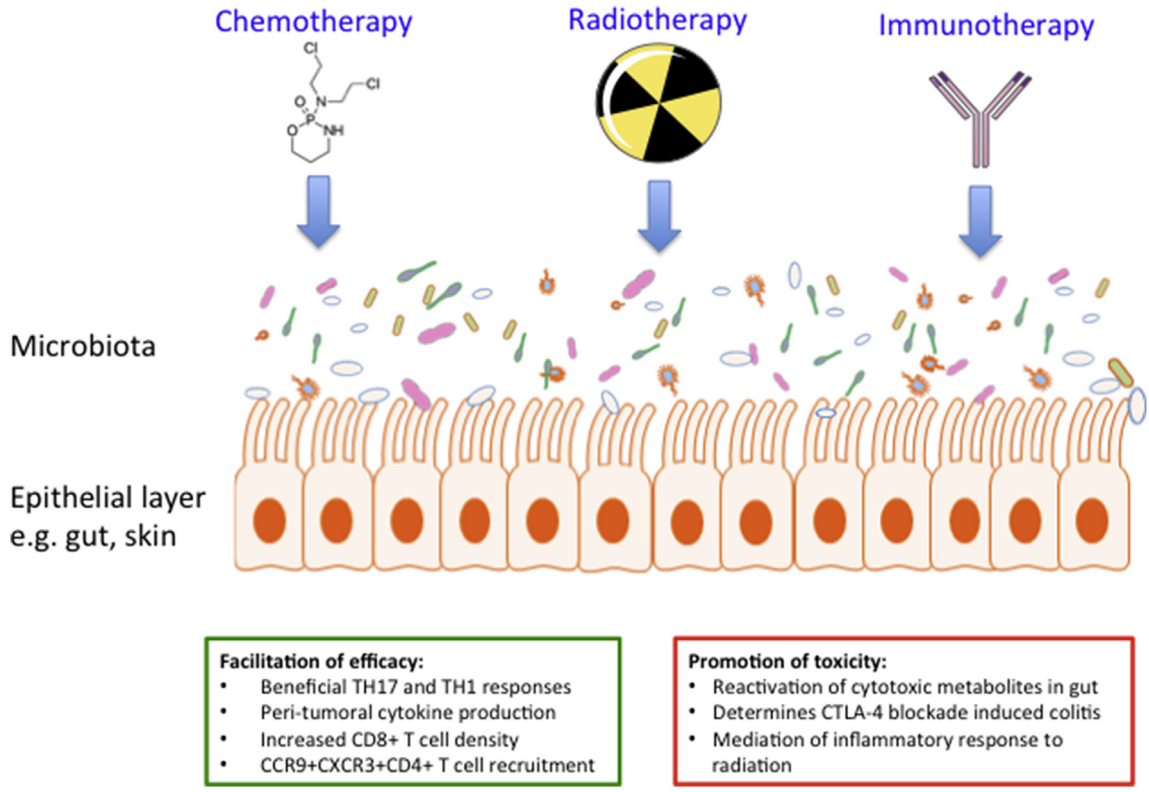


**Fig 1.** The microbiota are at the interface between cancer therapy and host responses.

## The Microbiota and Radiotherapy

There is currently a paucity of data on the potential impact of the microbiota on ionising radiation therapy. This is surprising, particularly given that radiotherapy causes damage of proliferating epithelia such as the gut and skin, which are the main sites of interface between host and microbiota. Radiation is known to alter the microbiota and there is some evidence from small studies that radiotherapy-associated toxicity can be predetermined based on gut microbiota profile [12,13]. In a mouse radiation proctitis model, irradiated mice developed a shift in mucosal microbiota with locally increased abundance of *Proteobacteria.* This microbial community potently induced inflammatory cytokines, such as interleukin-1β and tumour necrosis factor-α, and could transmit increased susceptibility to radiation-induced mucosal inflammation to germ-free animals [14].

## The Microbiota and Immunotherapy

The microbiota and host immune cells are in constant communication at a number of anatomical barrier sites, including the skin, respiratory tract and, most importantly, the gut. Resulting from this cross-talk are multitudinous effects on innate and adaptive immunity [15], and it is thus unsurprising that the microbiota should play a role in determining response to immunotherapy. Proof of this concept was provided by seminal work published in 2015 showing that the composition of the microbial communities colonising the gastrointestinal tract can impact on the efficacy of both CTLA-4 and anti-PD-L1 inhibitors in preclinical models of cancer [16,17]. In germ-free mice inoculated with MCA205 sarcoma, CTLA-4-specific antibodies failed to control tumour progression. However, in specific pathogen-free mice, CTLA-4 efficacy was restored, but could be nullified by treatment with broad-spectrum antibiotics [16]. Correspondingly, through the use of faecal transfer experiments, Sivan and co-workers [17] showed that favourable tumour response to anti-PD-L1 therapy was dependant on differential microbiota profiles in genetically similar mice.

A succession of subsequent clinical studies have shown that responders to anti-PD-L1 therapy can be differentiated from non-responders based on the composition of their pretreatment gut microbiota [18–20]. Notwithstanding the variability in taxonomic profiles of responders between studies (which may reflect geographical differences and the importance of shared function between compositionally distinct microbiota), each group was able to show that transfer of responder faeces to germ-free mice ameliorated anti-tumour efficacy of anti-PD-L1 treatment. Mechanisms included increased density of CD8+ T cells [18] and the recruitment of CCR9+CXCR3+CD4+ T cells to the tumour microenvironment [20]. In their cohort, Routy and Le Chatelier [20] showed that antecedent antibiotics prescribed for minor infections for 2 months before and up to 1 month after treatment with anti-PD-L1 had a deleterious effect on survival. Given the widespread use of antibiotics during the

typical cancer patient journey (from peri-surgical prophylaxis to treatment of immunosuppression-related infection), this should give us pause for thought.

Heterogeneity of patient response to immunotherapy also extends to toxicity. Susceptibility to CTLA-4 blockade-induced colitis appears to be protected against by microbiota of the *Bacteroidetes* phylum [21]. Interestingly, the enrichment of *Faecalibacterium,* a bacterium with anti-inflammatory properties [22], seems to be associated with both improved response to CTLA-4 blockade and increased likelihood of ipilimumab-induced colitis [23]. These seemingly dichotomous effects remind us of the intrinsic difficulty in trying to determine friend and foe in this multidimensional bionetwork (summarised in Table 1).

## Can We Exploit the Microbiota to Improve Patient Outcomes?

In the era of targeted therapies, the importance of personalised cancer medicine has never been more acutely felt [24]. On the one hand, accurately profiling the community composition of the intestinal microbiota could be used as a precision medicine tool to stratify patients according to their likelihood of responding. Moreover, the possibility of manipulating the intestinal microbiota to bolster anti-cancer therapies holds great promise in the coming years.

In a manner similar to the preferential use of cetuximab in KRAS wild-type cancers, it may be possible to stratify patients according to microbiota types to improve treatment responses and at the same time limit the risk of toxicity. As we have discussed, considerable challenges to implementation of the approaches exist. There is a lack of consistency between studies regarding which constituents of the microbiota are the key players [18–20]. Although some concerns persist about a lack of methodological standardisation in this evolving field of research [25], perhaps a more plausible explanation is the increasing awareness that microbiota composition is less important than their community function. Indeed, the function of a given bacterium can change depending on ecological niche. To answer this challenging question, oncologists need to work with microbiome scientists to embed microbiome research in large, prospective, longitudinal, multinational studies.

Manipulation of the microbiota for therapeutic benefit is a major goal. Probiotics have attracted much attention and there is some evidence that they may ameliorate treatment-related mucositis [26]. The spectrum of existing probiotics (comprising predominantly *Bifidobacterium* and *Lactobacillus* species) is relatively narrow and concerns persist about their use in the immunocompromised host. Consequently, there is currently limited evidence of benefit to cancer treatment efficacy.

A more radical approach is faecal microbiota transplantation, which has been used with remarkable success in the treatment of recurrent *Clostridium difficile* infection [27]. The concept is being tested in preliminary trials of autologous faecal microbiota transplantation for graft versus host disease as a means to reset the microbiota to a pretreatment state. More studies will surely follow.

Finally, a more prosaic target is the judicious use of antibiotics. Although in certain settings (e.g. neutropenic sepsis) broad-spectrum antibiotics are unavoidable, evidence implicating antimicrobials as drivers of poor response to immunotherapy [20] argues for limiting their use. Conversely, the finding that metronidazole used in mice bearing a colon cancer xenograft reduces cancer cell proliferation and tumour growth suggests that antimicrobials could be used as adjuvants to current therapies [28].

## Conclusions

There is incontrovertible evidence demonstrating that the intestinal microbiota has a profound impact on the host's phenotype, including susceptibility to illness and sensitivity to the therapeutic or toxic effects of treatment (more in depth reviews on this topic are available [29,30]). Robust and reproducible ways of characterising the microbiota, and ways of manipulating their composition, offer new clinical opportunities for precision medicine. However, challenges lie ahead in how we harness our growing knowledge of the microbiota to benefit cancer patients. The routine collection of faeces (regardless of tumour site) may be a hard sell to patients and healthcare colleagues alike, as

**Table 1**
Selected examples of microbiome interactions with cancer therapies

| Cancer therapy | Microbiota | Effect |
|---|---|---|
| 5-fluorouracil<br>Oxaliplatin | *Fusobacterium nucleatum* | Reduced HCT116 cell apoptosis through modulation of autophagy pathway |
| Cyclophosphamide | *Lactobacillus* | Stimulate TH17 and TH1 cell responses |
| | *Enterococcus hirae* | Increased intra-tumoral CD8/Treg cell ratio |
| | *Barnesiella intestinihominis* | Infiltration of interferon-γ-producing γδ-T cells |
| Irinotecan | β-glucuronidase producers | Release of toxic metabolite in the gut lumen |
| Radiotherapy | *Proteobacteria* | Enrichment in radiation proctitis |
| Anti-PD-L1 | Various | Increased density of CD8+ T cells |
| | | Recruitment of CCR9+CXCR3+CD4+ T cells |
| Anti-CTLA-4 | *Bacteroidetes* | Protective against CTLA-4 blockade colitis |
| | *Faecalibacterium* | Improved response to CTLA-4 blockade |
| | | Increased chance of CTLA-4 blockade colitis |

might the disruption of established treatment algorithms, such as the use of antibiotics. Improved stewardship of antibiotic use in many countries has yielded highly successful results in reducing the incidence of *Clostridium difficile* infection, hence adopting this approach holds some promise. Despite these challenges, it now seems inevitable that profiling and manipulating the intestinal microbiota will form part of the management strategies of a wide variety of diseases, including cancer.

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James Alexander: Nothing to declare.

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