Abstract from Malczewski AB, Ketheesan N, Coward JIG, Navarro S. Enhancing Checkpoint Inhibitor Therapy in Solid Tissue Cancers: The Role of Diet, the Microbiome & Microbiome-Derived Metabolites. Front Immunol. 2021;12:624434.

Keywords
Cancer immunotherapy · Checkpoint inhibitor therapy · Metabolome · Microbiome · Short chain fatty acids

Abstract
Host immunity plays a central role in the regulation of anti-tumour responses during checkpoint inhibitor therapy (CIT). The mechanisms involved in long lasting remission remain unclear. Animal studies have revealed that the microbiome influences the host immune response. This is supported by human studies linking a higher microbial richness and diversity with enhanced responses to CIT. This review focuses on the role of diet, the microbiome and the microbiome-derived metabolome in enhancing responses to current CIT in solid tissue cancers. The Western diet has been associated with dysbiosis, inflammation and numerous metabolic disorders. There is preliminary evidence that lifestyle factors including a high fibre diet are associated with improved responses to CIT via a potential effect on the microbiota. The mechanisms through which the microbiota may regulate long-term immunotherapy responses have yet to be determined, although bacterial-metabolites including short chain fatty acids (SCFAs) are recognized to have an impact on T cell differentiation, and may affect T effector/regulatory T cell balance. SCFAs were also shown to enhance the memory potential of activated CD8 T cells. Many therapeutic approaches including dietary manipulation and fecal transplantation are currently being explored in order to enhance immunotherapy responses. The microbiome-derived metabolome may be one means through which bacterial metabolic products can be monitored from the start of treatment and could be used to identify patients at risk of poor immunotherapy responses. The current review will discuss recent advances and bring together literature from related fields in nutrition, oncology and immunology to discuss possible means of modulating immunity to improve responses to current CIT.

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Knowledge Transfer

Background
Gut microbiota can be defined as all the species of bacteria, viruses, yeasts, fungi, protozoans, and archaea, as well as their genetics, that are found along the entire gastrointestinal tract. It is a research rising star, both in the preclinical and clinical arenas, and seen as a target capable of influencing many aspects of health and disease. A plant-based diet and its dietary components, namely its amount and variety of fibre, polyphenols, and fermented foods, have been linked to a positive impact on microbial diversity, which in turn has been associated with risk reduction of many chronic diseases, such as diabetes, cardiovascular disease, and cancer [1, 2]. While this knowledge continues to grow, and being multifactorial in nature, it has been partially linked to the gut microbiota and its metabolites, well known to be pleotropic and to widely influence health and disease development.

Checkpoint inhibitor therapy (CIT) is a relatively new treatment for certain cancers that has revolutionised treatment plans. It is more established in treatment regimens for malignant melanomas, renal cancer, and lung cancer, but its interest seems to be gaining traction in other oncology settings such as colorectal and triple-negative breast cancers to name a few. CITs have a different side effect profile than other cancer treatments, and, importantly, clinicians are still trying to understand why response rates vary and how to best improve them.

Review Discussions and Key Studies
Malczewski et al. review the evidence that a traditional lower-fibre, higher-processed Western-style diet is linked to dysbiosis, inflammation, and metabolic disorders, whilst emerging evidence shows that a high-fibre diet may be linked with an improved response to CIT due to improved microbial enrichment [3]. It is also discussed that an increase in short-chain fatty acid (SCFA) availability might enhance immune response via T cells. The authors also report evidence on therapeutic interventions such as fibre manipulation, use of pre- or probiotics, and faecal transplantation, their proposed roles in enhancing immune response, and their potential in modulating CIT response. This includes a study of 113 melanoma patients undergoing CIT, reporting that whole grains, fruits, and vegetables were associated with a ‘responder’ microbial signature, whilst sugars and processed meat had a negative association. These results help validate the current interest in understanding how a high-fibre diet might be associated with the best chance of response, and whether its effect might be explained through a putative increase in microbial richness [4]. Furthermore, there has been a recent surge in literature regarding probiotic strategies to modulate the gut microbiota in oncology. ESMO, MASCC, and ESPEN guidelines already consider that certain probiotic strains may be used to prevent chemotherapy/radiotherapy treatment-related diarrhoea [5–8]. In a recent systematic review, the use of probiotics during colorectal cancer treatment was deemed safe; however, the authors did not include any CIT clinical trials [9]. In contrast, other studies have found that probiotics might decrease the response to CIT, and there is a lack of evidence comparing each individual approach/strategy, e.g., probiotics vs. fibre, with regards to improved treatment response [10]. As with all emerging fields, more clarity as to the benefits of each approach is needed.

Conclusion for Clinical Practice
With dietary interventions being explored as a desirable strategy to enhance CIT response—a relatively inexpensive intervention especially when compared to the overall cost and treatment burden, should a blanket recommendation for dietary strategies such as high-fibre diets be considered? Unfortunately, we are not there just yet.

To the best of our knowledge, there are no current dietary guidelines for patients undergoing immunotherapy, and most preliminary evidence for dietary approaches must still be considered as emergent. Nutrition impact symptoms (NIS) relating to disease burden (e.g., obstructive symptoms) and/or other previous or concurrent anticancer treatment/s including CIT may increase with changes in dietary intake, especially food fibre content. Likewise, patients with a past medical history of certain gastrointestinal diseases (such as irritable bowel syndrome and inflammatory bowel disease), or those preparing and/or recovering from pelvic surgery, may develop or experience a flare in debilitating symptoms following a general recommendation to increase their intake of dietary fibre.

However, there is undeniable potential in an early multimodal intervention prior to treatment to improve baseline microbiota and support gut health. Ideally, this should be in the form of advice/recommendations on appropriately conditioning gut health, alongside a timely referral to a dietetic specialist to assist in managing uncontrolled NIS and side effects or, for example, tailor fibre intake modulation. In any case, careful patient identification for stratification of a beneficial approach is paramount and requires a multidisciplinary effort.

Disclosure Statement
We hereby confirm that there are no conflicts of interest with regards to this commentary.

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