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Commentary

Microbiome transplantation and modulation of immune related adverse events

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We recently cared for a 48-year-old male patient with stage IIIC (pT2aN3), BRAF V600E melanoma. After progression of disease on combination BRAF and MEK inhibitor therapy, he received combination immune checkpoint inhibitor (ICI) therapy with ipilimumab (anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) monoclonal antibody) and nivolumab (anti- programmed cell death protein (PD-1) monoclonal antibody). He developed treatment-limiting immune related colitis, managed with steroids and anti-TNF therapy, in addition to multiply relapsed *C. difficile* colitis, ultimately responsive to oral fidaxomicin. Whilst awaiting a clinical response to fidaxomicin, the infectious diseases and oncology team considered the role of faecal microbiota transplant (FMT) for the management of the multiply relapsed *Clostridioides difficile* colitis and of ICI-associated colitis and to improve responsiveness to further immunotherapy. The medical decision not to pursue FMT was based on recovery from *C. difficile* infection, absence of evidence as to the most favourable microbiome to optimise responsiveness to ICI and the lack of validated screening processes for donor stool to characterise the donated microbiome and exclude unintended consequences such as transfer of potential pathogens. During this time, the patient developed a belief that he needed to 'optimise' his microbiome via FMT. His decision was based on widely cited reports in the popular press about potential for improving the anti-cancer immune effects of ICI therapy via augmentation of the microbiome. Our patient was determined to seek an FMT and pursued this against medical advice, at a significant out-of-pocket expense. Unfortunately, despite FMT, the patient developed explosive disease shortly after FMT and the focus of his care was shifted to palliation.

The interactions between the host immune system and the colonising microbiota play an important role in both symbiosis and pathogenesis [1]. The gastrointestinal (gut) microbiome is implicated in immune modulation both locally and at distant sites [1]. We have seen explosive interest in microbiome modulation to treat gut diseases, such as *Clostridioides difficile* colitis and inflammatory bowel disease. There is also mounting evidence to support the role of the gut microbiome in shaping systemic ICI responses and modulation of immune related adverse events (irAEs) [2].

In pre-clinical murine models, Sivan et al. demonstrated that the gut microbiome can independently influence antitumor immunity and improve responsiveness to immunotherapy [3]. Further, Vetizou et al. demonstrated that disruption of the microbiome through the administration of broad-spectrum antibiotics reduced the antitumor efficacy of anti-CTLA-4 antibodies, but when followed by oral gavage with certain bacteria, was associated with restoration of anti-cancer responsiveness to ICIs. [4] Providing further support for the role of the microbiome modulating the anti-cancer systemic immune responses, Sivan et al. and Vetizou et al. both went on to demonstrate that mice that received FMT with human ICI responder microbiomes experienced superior intrinsic anti-tumour immunity and improved response to ICIs compared to mice that received non-responder FMT.

While there are significant differences between murine cancer models and patients, there is a growing body of evidence to suggest that findings from pre-clinical studies might be reproducible in humans. Gopalakrishnan et al. and others showed an association between a high diversity faecal microbiome and improved responsiveness to ICI therapy, which translated to prolonged progression-free and overall survival in a number of different cancer subtypes [5–7]. While these results are promising, there are important limitations too, including conflicting data regarding what organisms constitute a 'favourable' microbiome and inconsistencies between the various sampling, analytic and quantitation methods for interrogation of the microbiome, making comparisons between reports difficult. Furthermore, mechanistic

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insights into the role of the microbiome in anti-tumour immunity are lacking. Finally, the paucity of human data makes it impossible to make any meaningful recommendations to patients about the current role for augmentation of the gut microbiomes through FMT or other methods. So, while these findings highlight the therapeutic potential of gut microbiome modulating therapy for augmentation of anti-tumour immunity, this science is in its infancy.

The composition of the gut microbiome also appears to be linked to the development of irAEs. Vetizou et al. demonstrated that in mice with ICI-induced colitis, oral gavage with *Bacteroides* species led to reduced histological features of colonic inflammation [4]. In humans, certain bacterial phyla have been linked with both resistance to and the development of irAE, particularly those involving the gastrointestinal tract [8, 9]. There is significant overlap between organisms that are associated with higher rates of tumour response and higher rates of colitis; further understanding of the role of the microbiome in autoimmunity could translate into therapeutic strategies that uncouple toxicity from anti-tumour immunity. Wang et al. have been the first to describe two cancer patients with treatment refractory ICI-related colitis successfully managed with FMT from a single healthy donor [10]. However, on interrogation of the microbiome at the time of colitis and post FMT, the microbiomes of these patients were disparate, making it impossible to conclude which bacterial strains were responsible for either the colitis or its resolution. As important as it is to seek to define the ideal 'responder' microbiome it is equally important to define the 'at-risk-of-irAE' microbiome.

Trials are underway to assess the role for FMT and other microbiome modulating therapies in cancer patients. For example, a phase 1, single centre study of FMT from ICI responders into ICI refractory patients (NCT03353402). However, it is important to emphasise that there is currently insufficient clinical evidence to recommend any microbiome augmenting therapy to improve cancer outcomes outside of an investigational setting. Systematic, prospective interrogation of the gut microbiome using validated genomic assays in larger human cohorts is required before this knowledge can be translated into clinical practice [2]. Importantly, there is currently no clinical data to support the safety and efficacy of faecal transplantation for the purpose of achieving anti-tumour immunity. It is critical that both oncology and infectious disease clinicians have knowledge of this rapidly evolving area in order to carry out informed conversations regarding the limitations of current knowledge and potential for unintended consequences of FMT with this potentially vulnerable patient population.

Author contributions

Olivia C. Smibert: contributed to the structure, literature search and writing of the manuscript.

Christina W. Guo: contributed to the structure, literature search and writing of the manuscript.

Chloe Khoo: contributed to the structure, literature search and writing of the manuscript.

Karin A Thursky: contributed to the structure, literature search and writing of the manuscript.

Shahneen Sandhu: contributed to the structure, literature search and writing of the manuscript.

Monica A. Slavin: contributed to the structure, literature search and writing of the manuscript.

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