Editorial

The gut microbiome and its interaction with health, disease, treatment response and toxicity in patients advanced cancer: focus on lung cancer and immunotherapy

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The microbiome comprises a complex community of microorganisms that live symbiotically within hosts. In humans, the gut microbiome has the largest numbers of bacteria and the greatest number of species compared to other areas of the body (1). Research within this area has shown that both have co-evolved in a mutualistic relationship known to generate health and disease (2).

Changes in the microbiome flora have been shown to be implicated in the development of a diverse range of diseases such as obesity, type 2 diabetes, cardiovascular disease and autoimmunity such as inflammatory bowel disease, asthma, rheumatoid arthritis (2).

In the field of Oncology, specific bacteria have been shown to be involved in carcinogenesis. The microbiome has also been shown to influence the efficacy and toxicity of some anti-cancer therapy (2). Preclinical and early clinical data suggest that modifying the host's microbiome could improve the efficacy of immunotherapy for cancer and become a novel biomarker for modulating and enhancing response, especially in patients treated with CTLA-4 and PD-(L)1 checkpoint blockade (3-7).

Metagenomic studies to date have primarily used 2 ways of identifying particular bacterial communities. The most common low cost and high throughput method is selective amplification and sequencing of a part of the gene encoding part of the small ribosomal subunit in this species, the 16S ribosomal RNA. This method is usually limited to a family or genus level. The second most commonly used method is metagenomic shotgun sequencing which generates short reads representing the whole genomic content. This is considered superior to 16S rRNA sequencing as it can identify down to species level and can also be used to characterise non-bacterial organisms (2).

A number of studies to date have shown a correlation between the gut microbiome and demonstrated that this can influence the effects of immunotherapy and some chemotherapy. An early mouse study showed the gut microbiome is essential for optimal responses to CpG-oligonucleotide immunotherapy which activates immune cells through toll like receptor 9 signaling (8). Another mouse model showed that Cyclophosphomide alters the composition of microbiome in the small intestine and induces the translocation of species of Gram$^+$ bacteria into secondary lymphoid organs. These bacteria stimulate the generation of a specific subset of "pathogenic" T helper 17 (pTh17) cells and memory Th1 immune responses which influence the response to cyclophosphomide (9).

Pioneering work in the field of immuno-oncology with CTLA-4 and PD-(L)1 checkpoint blockade found that the anti-tumour effects of these agents are modulated by distinct bacterial species. Tumours in antibiotic treated or germ free mice did not respond to checkpoint blockade and this primary resistance was overcome by gavage of specific micro-organisms or faecal microbial transplant. These studies established the link between the microbiome and immune checkpoint blockade and inspired clinical quests to add to the growing evidence, in particular further correlative metagenomic analyses (3-7).

Katayama *et al.* investigated the role of the gut microbiome on the efficacy of immune checkpoint inhibitors (ICIs) in a small single center cohort of 17 Japanese patients (10). This study included patients diagnosed with non-small cell lung cancer (NSCLC) and only included patients who had received treatment with ICIs for over 3 months. The authors collected stool samples on one occasion between June 2017 and March 2018 from each patient and performed 16S rRNA, performing statistical analyses and correlating these with response defined as partial response to treatment according to RECIST 1.1 or no response [stable or progressive disease (PD)]. Results from the study revealed the gut microbiomes of responders were significantly rich with *Lactobacillus*, *Clostridium*, and *Syntrophococcus* when compared to non-responders. Gut microbiomes of the non-responders were significantly rich with *Bilophila*, *Sutterella*, and *Parabacteroides*. Patients with a high abundance of *Lactobacillus*, *Clostridium*, and *Syntrophococcus* tended to have a longer time to treatment failure (TTF). Patients with a low amount of *Bilophila* and *Sutterella* had a significantly prolonged TTF. Unlike other published studies, the alpha-diversity of the gut microbiota was not significantly different between the responders and non-responders and did not influence the TTF. However, the absolute numbers to achieve statistical significance are very low.

Previously published studies have revealed a specific bacterial landscape that appears more common in patients who respond to treatment, whereas other bacterial sequences appear to be over-represented in non-responder patients. These discrepancies could be multifactorial, ranging from inter-patient variability due to previous differing therapy, medications, diet, geographic location or other genetic factors. The recurrent species which appear to be correlated with response across studies are *Faecalibacterium*, *Bacteroidales*, *Ruminococcaceae*, *Clostridiales*. Not all of these are mentioned in this study (11).

Katayama and colleagues did not give insights on sequential testing of samples which can change throughout time and could potentially generate a differing response to immunotherapy or lead to treatment failure. It would be interesting to know whether the microbiome is any different at treatment failure compared to at the start and what could lead for this dysbiosis to happen.

It could also be seen as biased towards responders in view of the inclusion of patients on treatment for over 3 months. In addition, the group selected had generally a good performance status, PS 0-1 which could also select bias towards patients who will overall be more likely to benefit. This can be seen in the higher response rates achieved compared to responses seen in other studies. The authors very astutely took into account use of corticosteroids and antibiotics in their analysis however the numbers are too small to look for any significant differences. There is no mention of whether patients with brain metastases were included in this study.

Stable or progressive disease (as per RECIST criteria) at the time of 1st clinical evaluation on ICIs could be difficult to interpret in cases of pseudo-progression. The use of irRECIST is not mentioned. A number of patients with stable disease were classed as non-responders however if these patients had prolonged periods of stable disease it is possible they could be responding patients.

Given the complexity of the gut microbiome and its interaction with health, disease, treatment response and toxicity, it can be complex to translate definite results into patient outcomes. Even if individuals possess the same bacterial strain, there can be differences in how these interact with the rest of the microbiome, therefore caution is advised when assigning attributes to particular bacteria. A recent trial which led to *E. Coli* septicaemia post Faecal microbial transplant has recently re-started after a Suspected Unexpected Serious Adverse Reaction (SUSAR) highlighting the importance of remaining vigilant when researching new therapies (12). In addition, studies have focused on the bacterial components of the microbiome and not on fungi, viruses or protozoa.

Sadly, despite attempts to understand and enhance immunotherapy responses, cancer cells grow and mutate with different therapies and it likely that the microbiome is just one of the factors at interplay. Further large scale prospective studies investigating the gut microbiome and its effect efficacy of ICIs are ongoing and results are eagerly awaited.

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