Is gut microbiome a predictive marker to response to immune checkpoint inhibitors?

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First draft submitted: 15 July 2017; Accepted for publication: 7 August 2017; Published online: 15 September 2017

Keywords: gut microbiome • immune checkpoint inhibitors • predictive marker

Immune checkpoint inhibitors (ICI) are changing the treatment of solid and hematologic malignancies and becoming an integral part of the management of cancer patients. Ipilimumab, a CTLA-4 inhibitor, was associated with significant survival benefit in metastatic melanoma [1]. In addition, PD-1 and PD-L1 inhibitors such as nivolumab, pembrolizumab and atezolizumab showed remarkable clinical responses in multiple cancer types ranging from 20 to 30% when used in monotherapy. These agents are approved by the US FDA in the management of various tumor types such as metastatic melanoma, non-small-cell lung cancer (NSCLC), renal cell carcinoma, classical Hodgkin's lymphoma, urothelial bladder carcinoma and squamous cell carcinoma of the head and neck [2]. Identifying reliable biomarkers for efficacy would be of interest to improve the outcome and overcome resistance.

Several candidate biomarkers had been explored including immunological ones such as intratumoral lymphoid infiltrates and intratumoral PD-L1 expression, genetic biomarkers like oncogenic mutations, mutational load and DNA-mismatch repair deficiency [3]. Recently, emerging data show that gut microbiome might affect the efficacy of ICI making it a potential biomarker of response. In addition, the manipulation of the microbiome by broad-spectrum antibiotics leads to increased susceptibility to infections, accumulation of antibiotic resistances, deregulated metabolism and compromised immune homeostasis [4].

Recent reports focused on the role of microbiome in the response to ICI. It was first evaluated in murine models and preclinical studies showed the contribution of gut microbiome in the efficacy of ICI. Vetizou *et al.* demonstrated that tumor progression of sarcomas in mice housed in specific pathogen-free condition was inhibited with anti-CTLA-4 in contrast to mice housed in germ-free (GF) condition [5]. In addition, the use of broad-spectrum antibiotics such as colistin and imipenem to eliminate gut microbiota altered the antitumor effect of CTLA-4 inhibitors. It was also confirmed in melanoma and colon cancer models. Moreover, the activation of splenic lymphocytes and tumor-infiltrating lymphocytes mediated by anti-CTLA-4 was significantly decreased in GF and antibiotic-treated mice [5]. When researchers recolonized GF mice and antibiotic-treated mice with bacterial species they found that anti-CTLA-4 anticancer responses could be restored with *Bacteroides fragilis*, *Bacteroides thetaiotaomicron*, *Burkholderia cepacia*, or the combination of *B. fragilis* and *B. cepacia* via stimulation of Th1 immune response [6].

In a prospective study, 26 patients treated with ipilimumab for metastatic melanoma were enrolled. The authors found that anticancer response was associated with colonization by Firmicutes and specifically by *Faecalibacterium prausnitzii* L2–6, butyrate producing bacterium L2–21 and *Gemmiger formicilis* ATCC 27749. Patients having microbiota enriched with *Faecalibacterium* genus and other Firmicutes had significantly higher progression-free survival (PFS) ($p = 0.0039$) and overall survival (OS) compared with patients having initial microbiota enriched with bacteroidetes. They also found higher proportion of these bacteria in all patients having overall survival longer than 18 months [7]. In contrast to Vetizou *et al.* findings, patients who had poor clinical response to ipilimumab presented higher representation of bacteroidetes (mostly bacteroidetes genus). It can be attributed to a bias in the reconstitution of microbiota in mice using human fecal microbiota transplantation [5,7].

Recent report evaluating the microbiome in patients treated with PD-1 inhibitors in metastatic melanoma showed that diversity and composition of gut microbiome was significantly different in patients responding to anti-PD-1 compared with those who do not respond. The diversity was significantly higher in responders versus

nonresponders ($p = 0.03$). Furthermore, the composition of gut microbiome was different between the two groups; Clostridiales were more abundant in responders however Bacteroidales were more frequent in nonresponders [8]. These findings were consistent with Chaput *et al.* results concerning the possible adverse role of initial bacteroidetes colonization [7,8]. On the other hand, it has been demonstrated that tumor immune infiltrates including CD8⁺ T cells were increased in responders. In addition, diversity and abundance of specific bacteria were associated with higher PFS in response to PD-1 inhibitors ($p = 0.009$ and $p = 0.007$ respectively) [8].

Since, broad-spectrum antibiotics can affect 30% of gut microbiota, their effect on ICI efficacy was retrospectively evaluated in patients having advanced renal cell carcinoma, urothelial carcinoma and NSCLC and treated with anti-PD1/PD-L1. The duration of antibiotic use was defined as 2 months before treatment with ICI or within first month of receiving these agents. Out of 175 patients analyzed, 51 patients (29%) received antibiotics. β -lactam and fluoroquinolones were the mostly used antibiotics. Researchers found that median PFS and OS was significantly shorter in patients receiving antibiotics compared with those who do not receive (3.4 vs 5.2, $p < 0.013$ for PFS and 12.2 vs 20.8 months, $p < 0.001$ for OS). It has been also demonstrated that patients having NSCLC and receiving antibiotics had significantly shorter OS compared with the other group (7.0 vs 13.8 months, $p = 0.038$). Furthermore, median PFS was significantly lower in patients having renal cell carcinoma and urothelial carcinoma and receiving antibiotics (4.3 vs 7.4 months, $p < 0.013$ and 1.8 vs 4.3 months, $p = 0.048$, respectively). On multivariate analysis, this negative impact of using antibiotics prior to immunotherapy was maintained [9]. Determining more predictive markers to immune checkpoint inhibitors is necessary to stratify the patients into responders and nonresponders. Gut microbiome represents an interesting landscape to explore as predictive marker to immune checkpoint inhibitors, with promising preliminary results. Larger prospective trials should be performed to confirm these results.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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