Editorial

# Does the gut microbiota play a key role in PD-1/PD-L1 blockade therapy?

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Immune checkpoint inhibitors (ICIs), including anti-programmed cell death-1 (PD-1) and anti-PD-ligand-1 (PD-L1) antibodies have revolutionized the treatment of lung cancer. Most advanced lung cancer patients without driver mutations receive ICIs or ICIs combined with chemotherapy as a first line treatment. Although 10–40% of non-small cell lung cancer (NSCLC) patients have durable responses to ICIs, approximately 30–40% of patients show disease progression 6–8 weeks after the start of ICI treatments if they are treated with anti-PD-1/PD-L1 monotherapies (1,2). To select patients most likely to respond to ICI treatment, predictive biomarkers have been extensively explored. The expression of PD-L1 on tumor cells is the most established biomarker for anti-PD-1 therapy. However, there are unresolved problems regarding the use of PD-L1 expression as a predictive biomarker, including intratumoral heterogenic expression of PD-L1, dynamic changes in PD-L1 expression during cancer treatments, and the unresponsiveness of patients even when their tumors express high levels of PD-L1.

The gut microbiota plays an important role in gut health to enhance epithelial barrier integrity and protect against pathogens. The interactions between the gut microbiota and the host immune system have been reported (3,4). Recent studies have demonstrated the association between the gut microbiota and the antitumor effects of ICIs. Sivan *et al.* found the enhancement of spontaneous antitumor immunity and antitumor efficacy of anti-PD-L1 antibodies in mice with a specific species of bacteria, *Bifidobacterium* in the gut (5). Dendric cell function and the accumulation of $CD8^+$ T cells in the tumor microenvironment were increased in mice with *Bifidobacterium*. Similar correlations between the gut microbiota and antitumor efficacy of PD-1/PD-L1 blockade therapy have been reported in human cancer patients. The fecal samples from NSCLC patients who were enrolled in the CheckMate 078 and the CheckMate 870 trials and received nivolumab were analyzed (6). High microbiota density and the enrichment of *Alistipes putredinis*, *Bifidobacterium longum* and *Prevotella copri* were associated with improved outcomes, whereas the enrichment of *Ruminococcus_unclassified* was correlated with poor responses to anti-PD-1 antibodies. Routy *et al.* evaluated 249 patients, including 140 NSCLC patients, and found that 69 patients (28%) were administered antibiotics 2 months before and 1 month after the start of anti-PD-1/PD-L1 therapy (7). These 69 patients had significantly worse survival than patients who did not receive antibiotics (median overall survival 11.5 versus 20.6 months, P<0.001). The authors further found that the transplantation of fecal microbiota from cancer patients who responded to ICI treatments, but not from nonresponders, into germ-free mice improved tumor control. This relationship between the gut microbiota and the antitumor effects of anti-PD-1/PD-L1 therapy is supported by other researcher results (8,9). The following possible mechanisms underlying the modulation of antitumor immunity by the gut microbiota

were suggested: the activation of IFN-γ pathways, production of IL-12, induction of the Th1 immune response in the tumor-draining lymph nodes through the activation of dendritic cells (DCs), and the maintenance of regulatory T cells (5,7,10,11).

In *Translational Lung Cancer Research*, Yuki Katayama and colleagues reported a retrospective study evaluating the association between the gut microbiota and the antitumor effects of PD-1 blockade therapy using linear discriminate analysis coupled with effect size measurements (12). They collected stool samples from 17 patients who were treated with anti-PD-1 therapy. Previous studies reported that several species of bacteria in the gut microbiota are associated with good clinical outcomes following ICI. Katayama *et al.* newly found that patients with highly abundant *Lactobacillus*, *Clostridium* and *Syntrophococcus* tended to have an increased time to treatment failure with anti-PD-1 monotherapy, whereas patients with an increased abundance of *Bilophila* and *Sutterella* tended to have a decreased time to treatment failure. The authors suggested that *Lactobacillus* promotes DC maturation and mediates antitumor immunity. Because several factors including genetic background, the environment and food culture, could affect the composition of the gut microbiota and the interaction between the microbiota and antitumor immunity in cancer patients, further studies and the accumulation of data from various regions are warranted.

Recent evidence has demonstrated that immune-related adverse events (irAEs) are also affected by the gut microbiota. Liu *et al.* reported an association between immune-related diarrhea and the gut microbiota (13). They analyzed fecal samples from 26 lung cancer patients and found that patients with immune-related diarrhea had a significantly greater abundance of *Veillonella* than patients without diarrhea. In contrast, significantly reduced amounts of *Parabacteroides* and *Phascolarctobacterium* were detected in patients with diarrhea. Chaput *et al.* categorized metastatic melanoma patients receiving ipilimumab, anti-cytotoxic T-lymphocyte-associated antigen 4 antibodies, according to the composition of the gut microbiota (14). Patients with cluster A, which was enriched in *Faecalibacterium* and other *Firmicutes*, had better outcomes than patients with cluster B, which was enriched in *Bacteroides*. In addition, belonging to cluster A was associated with a reduced colitis-free cumulative incidence. The authors further demonstrated that patients with immune-related colitis had a reduced percentage of Tregs and reduced levels of IL-6, IL-8 and soluble CD25 before the start of ipilimumab treatment. The authors suggested that the serum levels of systemic inflammatory proteins at baseline might reflect the composition of the gut microbiota and predict the development of ICI-induced colitis.

Preclinical models have shown that the administration of specific kinds of bacteria improves the outcomes of tumor-bearing hosts. Tanoue *et al.* isolated 11 bacterial species from healthy human donors that are able to stimulate DCs and induce IFN-γ producing $CD8^+$ T cells in the intestine (15). Transplantation of these 11 strains into tumor-bearing mice resulted in the augmentation of the antitumor effects of ICIs. A number of clinical studies are ongoing to investigate whether the transplantation of microbiota from responders to ICIs effectively increases the antitumor effects of ICIs. Interestingly, some of these studies are evaluating the effects of microbiota transplantation on chemo-immunotherapy.

Although immunotherapy is a game changer for the treatment of lung cancer, not all NSCLC patients benefit from ICIs. Further prospective studies are warranted to not only develop a predictive biomarker for ICIs but also develop a new combinational strategy consisting of ICIs and the modulation of the gut microbiome.

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*Ethical Statement*: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.



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