Editorial

Antibiotics in cancer patients: is the verdict still out?

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Immune checkpoint inhibitors (ICI) have shown tremendous successes on treatment of multiple tumor malignancies, offering a valuable but rare commodity to both patients and researchers (1-3). As an important part of tumor immunotherapies, ICIs inspire the once-questioned idea that although inhibited our immune system is able to eliminate tumor cells in a similar way that it does to infectious microorganisms. ICIs can release the brakes imposed by the tumor on this fabulous capability, which then heightens the immune response against tumor cells. Two of the best studied ICIs aim at the cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) signaling and the programmed death-1 (PD-1) protein signaling, which exhibit high efficacy against advanced melanoma, non-small cell lung cancer (NSCLC) and renal cell carcinoma (RCC). Moreover, the anti-tumor effects of these ICIs are synergistic, as the combination of ipilimumab, an FDA-approved CTLA-4 antagonist, and nivolumab, an FDA-approved PD-1 inhibitor, exhibit superior objective response rate (ORR) and overall survival (OS) (4).

Tough challenges of ICI therapies include why some patients, but not all, benefit and how positive responses could be durable. In a Phase III study of ipilimumab and nivolumab combination therapy of advanced melanoma patients, the ORR was 58% for the combination group, 44% for the nivolumab group and 19% for the ipilimumab group. The rate of complete response (CR) was 19% for the combination group, 16% for the nivolumab group and 5% for the ipilimumab group (5). The failure of ICI response has been attributed to poor immunogenicity of tumor cells (6,7), defective antigen presentation during the priming phase (8) and the absence of functional tumor-infiltrating lymphocytes (9,10). Tumor mutational burden (TMB) increases immunogenicity of tumors and hence has been proposed as a biomarker for response to anti-PD-1 therapy based on an extensive ORR analysis by a John Hopkins team from an extensive literature search covering 27 tumor types (11), and the latest update of checkmate-032, an ongoing phase I/II trial, from the International Association for the Study of Lung Cancer (IASLC) 18th World Conference on Lung Cancer by Bristol-Myers Squibb (BMS).

Factors beyond tumor genomics such as microbiomes have also been reported to influence tumor treatment outcomes. *Mycoplasma hyorhinis*, a pathogenic commensal bacterium, metabolizes the chemotherapeutic drug gemcitabine, commonly used in pancreatic ductal adenocarcinoma treatment, into its inactive form and eventually contributes to drug resistance of these tumors (12). Preclinical studies in mice suggest that gastrointestinal microbes can shape responses to ICI therapies. Two new studies published on November 2, 2017 in Science provide direct evidence highlighting the role of our body's resident microbes in PD-1 based immunotherapies (13,14). Such data raise the question whether we should be limiting or tightly monitoring antibiotic use in these therapies.

Dr. Gopalakrishnan and colleagues from MD Anderson Cancer Center analyzed oral and fecal samples from 112 patients with advanced melanoma prior to anti-PD-1 treatment, using 16S ribosomal RNA (rRNA) sequencing to profile the microbiomes according to their unique genetic signatures (13). At 6 months after treatment initiation, patients were classified as responders or non-responders

according to radiographic assessment with response evaluation criteria in solid tumor (RECIST 1.1). Examination of the fecal, but not oral, samples revealed that the patients with diverse microbiomes were likely to respond to the PD-1 inhibition. More specifically, the responder group showed significant enrichment of Clostridiales/Ruminococcaceae, especially *Faecalibacterium* genus, while non-responder group showed preference to Bacteroidales. The presence of the *Faecalibacterium* and Clostridiales bacteria seemed to account for the strong antitumor immune response, as both the responder group and the recipient mice by fecal microbiome transplantation (FMT) from the responders had higher density of immune cells infiltrating the tumor mediated by increased antigen presentation and improved tumor killing.

Another study led by Dr. Laurence Zitvogel, scientific director of the Gustave Roussy Cancer Center in France, focused on the impact of gut microbiome dysfunction on ICI therapy. In a mouse model with established MCA-205 sarcoma and RET melanoma, broad-spectrum antibiotics treatment significantly compromised anti-PD-1 and anti-CTLA-4 antibody efficacies and the survival of treated mice. Analysis on patients who had taken antibiotics within 2 months before, or 1 month after, the first administration of anti-PD-1/PD-L1 monoclonal antibody found that both progression-free survival (PFS) and OS were significantly reduced. Gut microbiota profiles derived from quantitative metagenomic shotgun sequencing identified an overrepresentation of *Akkermansia muciniphila*. The commensal gut microbe, exerting profound influence on host metabolism and immunity, was found to associate with beneficial clinical outcome. FMT with responder stool reinitiated an anti-tumor effect of PD-1 blockade in microbiome-depleted mice. Consistently, recolonization with *A. muciniphila* alone or together with *Enterococcus hirae* reversed the compromised efficacy of PD-1 blockade from either antibiotics treatment or germ-free farming. The researchers further found that the favorable microbes helped to accumulate CCR9+CXCR3+CD4+ T lymphocytes, increase the active/repressive T cell ratio and boost immunogenicity by IL-12.

These two studies are extension work of previous researches in mice and provide intriguing insights into the influence of microbiome on tumor immunotherapy. We found several strengths in these studies. Dr. Zitvogel's study includes a direct comparison between antibiotics treated and untreated patients under PD-1 blockade therapy. The difference here means that most, if not all, of us have "good" microbes in our bodies, which indeed help maintaining a certain level of anti-tumor immune response. This information raises concerns of the use of antibiotics in tumor immunotherapies, which undermines such vulnerable contributions from the "good" microbes. Meanwhile, the microbiome profiles from both studies point out that the level of "good" microbes could be quite different among individuals. Companion diagnostics on gut microbe composition and supplement of "good" microbes might be auxiliary treatment for ICI therapy in the future. Diverse "good" microbes identified in the two studies, probably due to geographical separation and different life styles, suggest a multiple choice of such probiotics.

An interesting question here is whether there are some "bad" microbes, whose existence may place negative influence on ICI or other immunotherapies. Both studies identify candidates of "good" microbes and the beneficial outcome of the recolonization process. Then it would be quite reasonable to propose that some other microbes might activate immune response in an opposing way, cultivating a favorable environment for tumor growth. Recolonization of the overrepresented microbes from non-responder group in germ-free or antibiotics treated mice would be helpful to distinguish such "bad" microbes, strategically eliminating which could wipe out the repression and transform non-responder to responder.

Although two independent, well-done studies come to similar results, it might still be too soon to interpret that as "stop antibiotics" or "supplement 'good' microbes" for tumor patients. Their work is a great step forward beyond previous mouse work, offering the data from the human patients, but also begs the next question—"What are the microbes doing?"

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