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EDITORIAL

The hope of modulating microbiome in the management of cancer patients

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Human beings harbor tens of trillions of bacteria in their bodies[1]. The majority of these bacterial colonies found either on the skin surface or inside the guts are typically benign or even beneficial. Using the human fecal samples of a cohort of 124 healthy individuals for metagenomics deep sequencing analysis, an estimate of 1000 to 1150 prevalent bacterial species was found. Among these bacterial species, 160 are shared by all the individuals[2]. It is known that long-term dietary intake can impact the composition and activity of microorganisms in the human gut[3,4]. However, how the actual bacterial community (microbiota) or microbiome (the genetic content of these bacteria) affects the health state of an individual remains unknown. Recently, the stories of the association of a specific microbiome with tumor progression and immunotherapeutic responses are beginning to unfold.

Recent studies have shown that gut microbiota is an important factor that can modulate host immunity and thus immune therapeutic responses. In the first case reported last year, it was demonstrated that the gut microbiota composition at baseline before immunotherapy treatment could be an indicator to predict significant patient response to the immunotherapeutic drug, ipilimuab[5]. In the last few months, three studies provide additional evidence that the intestinal microbiota affects the outcome of anti-PD1 immunotherapy in patients with cancer[6-8]. In the first study by Routy *et al*., they investigated interactions between PD1-based immunotherapy and the gut microbiota in individuals with epithelial tumors. A more diverse intestinal microbiome was found in responders than non-responders. Two bacterial species *Akkermansia muciniphila* and *Enterococcus hirae* are much higher in anti-PD1 treated lung cancer patients[6]. In the second study by Gopalakrishnan *et al*., significant differences were also observed in the diversity and composition of the gut microbiome of responders (n=30) versus nonresponders (n=13) from melanoma patients undergoing anti-PD1 immunotherapy. Responding patients had a significantly higher diversity and relative abundance of bacteria of the Ruminococcaceae family than non-responders. Whole genome sequencing further confirmed a high abundance of *Faecalibacterium* species in responders. To demonstrate the importance of the microbiome in modulating the above responses, germ-free mice received fecal transplants from responding patients and were found to have a higher abundance of *Faecalibacterium*, CD45+ immune cell and CD8+ T cells. These mice also had smaller BP melanoma tumor size than those mice receiving fecal transplants form non-responders[7]. In the third study by Matson *et al*., using metagenomics analysis of bacterial microbiome from pre-treatment stool sample of metastatic melanoma patients, it was found that bacterial species, such as *Bifidobacterium longum*, *Collinsella aerofaciens*, and *Enterococcus faecium*

are more abundant in anti-PD1 responders. Similarly, through the reconstitution of germ-free mice with fecal material from responding patients, it was found that mice with a reconstituted microbiome from anti-PD1 responders had a better tumor control of implanted B16.SIY melanoma cancer cells and greater efficacy of anti–PD-L1 therapy than those reconstituted with microbiome from non-responders[8]. The importance of microbiome diversity was previously demonstrated using an azoxymethane/dextran sodium sulfate induced colorectal tumorigenesis mouse model[9]. Transfer of the gut microbiome from wild-caught Maryland mice to germ-free C57BL/6 laboratory mice significantly increased microbiome diversity and reduced the number of tumors induced[9]. Thus, microbiome diversity might be important in cancer prevention. These data provide hope for the potential use of microbiome modulation to augment the efficacies of immune checkpoint inhibitors on patients.

On the other hand, interestingly, it was found that the majority of human pancreatic tumors contained bacteria that could convert the drug gemcitabine into an inactive metabolite that led to drug resistance in many cases[10]. Moreover, some intestinal bacteria can migrate from the gut to the pancreas and adversely influence the pancreatic microenvironment by inducing intratumoral immune suppression[11]. Using a genetic pancreatic mouse model (KC mouse) that progressively developed pancreatic cancer, it was found that *Bifidobacterium pseudolongum* was the most abundant fecal *Bifidobacterium* species identified in this model. Similarly, Proteobacteria phyla also constituted nearly 50% abundance in the human cancerous pancreas but only constituted 8% of the microbiome in the gut of these patients[11]. Surprisingly, oral antibiotic administration slowed oncogenic progression of KC mice and enhanced antitumor immunity and susceptibility to immunotherapy[11]. In conclusion, different species of the same *Bifidobacterium* genus might have opposite effects on tumor progression.

As both commensal bacteria and tumor factors can alter the magnitude of endogenous immune priming and T cell infiltration into the tumor microenivironment, the cross-talks between specific bacterial species and the epithelial cells or immune cells will need to be clearly defined. It is time to generate a more definitive bacteria-immune interaction profile. A recent study indicates that approximately 90% of the bacterial species are culturable[12]. Thus, it is possible now to study the contribution of individual bacterial species to tumor progression, initiation, immune suppression or enhancement of cancer immunotherapy by culturing individual bacterial species for functional studies. In principle, this kind of study should focus on an individual with a diverse microbial composition that includes bacteria associated with both favorable and unfavorable treatment outcomes. Therefore, metagenomic and metatranscriptome analysis of microbial community diversity and metabolic activities could be best studied by using rRNA sequencing and shot-gun RNA sequencing[13]. The central challenge of modulating the gut microbiome is how to boost host immunity without causing potential adverse effects associated with certain bacteria. Modulation of the host gut microbiota has a promising future for cancer intervention. Metagenomic analysis of stool samples might soon be a standard test for monitoring the cancer risk and treatment response of an individual.

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