Role of the Gut Microbiome in the Modulation of Cancer Immunotherapy Response

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The gut microbiome or gut flora is a vast community of microorganisms such as bacteria, viruses, protozoa, and fungi that inhabit the digestive tract of the human and other animals [1,2]. In the human body, bacterial species colonize into the oral cavity, skin, vagina, and placenta, however, the largest population of microorganisms resides in the intestine. The majority of gut microbiota belong to the phyla Firmicutes, Bacteroidetes, Proteobacteria and Actinobacteria [2]. Colonization of the gut microbiota begins during or after the birth when the neonates get exposed to the vaginal microbes as he or she passes through the birth canal of the mother [3,4]. The growth and population of the gut microbiome are influenced by multiple factors including gestational age, mode of delivery (vaginal/cesarean), infant feeding method, diet, environment, medications, exposure to antibiotics, and comorbid diseases [2,5-8]. Gut microbiota has co-evolved with humans for millions of years to form a mutually beneficial relationship. They play important role in food digestion, nutrient and mineral absorption, synthesis of amino acids, enzymes and vitamins, and production of short-chain fatty acids, thus crucial for health and wellbeing [9,10]. Also, the gut microbiota is involved in immune regulation, brain function, and neuroendocrine responses [11,12]. The human gastrointestinal tract harbor both unhealthy and healthy microbiota, that arise through a complex combination of genetic, environmental, and lifestyle factors. Their imbalance contributes to high blood sugar, high cholesterol, weight gain, and other pathological conditions [11,13]. Change in the population of normal microbiota has been suggested to associate with the development and progression of many diseases [13]. Several species of bacteria including *Helicobacter pylori* and *Coriobacteriaceae* have been identified as potential candidates associated with carcinogenesis [14,15].

The immune system is the key to protect the host from invading pathogens such as bacteria and viruses, as well as tumor cells that appear through several mutations. To keep the activity of the immune system in control and to avoid the autoimmune reactions, the host body has developed several immunosuppressive mechanisms [16,17]. The cancer cells selectively exploit these immunosuppressive or checkpoint mechanisms to evade immune eradication. The programmed cell death protein ligand 1 (PD-L1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) receptor B7 expressed by tumor cells restrict the activity of the immune cells. The special class of therapy knows as checkpoint inhibitor immunotherapy unleashes the brake of the immune system by targeting cell-surface molecules to revive antitumor immunity [17,18]. The PD-L1/PD-1 and CTLA-4 checkpoint inhibitors/antibodies have shown remarkable antitumor responses in the clinic [17,18]. A growing body of evidence indicated that the gut microbiota influences the tumor growth and progression by modulating the immune system activity [19-22]. The gut microbiota released cytokines and growth factors regulate the immune system's response to cancer [23]. Several bacterial species that reside in the gut have been associated with favorable and improved tumor-immune responses of checkpoint inhibitor immunotherapy [19-22]. Also, the recent findings have indicated that the balance of microorganism's population is also an important factor in the induction of anti-tumor immune response. The role of microbial products in cancer care has been explored over a century ago by Coley after inoculating the mixture of heat-killed *Streptococcus* pyogenes and *Serratia marcescens* in the patients with bone and soft-tissue sarcomas as a

cancer vaccine candidate. Significant progress in our understanding attributed to the advancement in the research, we have identified several microbes that regulate an anti-tumor immune response [24,25]. These are significant and very important findings that could lead to the development of novel and improved therapeutics to manage cancer by altering the composition of gut microbiota.

Sivan et al. observed two genetically similar C57BL/6 mice procured from two different vendors [Jackson Laboratory (JAX) and Taconic Farms (TAC)] had differences in the rate of melanoma growth, tumor-infiltrating lymphocyte response, and CD8+ T cell numbers [19]. These dissimilarities abolished after cohousing, raised the speculation that microbiota might be participating in the differential anti-cancer effects. This hypothesis was verified by transferring the JAX or TAC fecal material from one mouse to another by oral gavage before the tumor implantation in these animals [19]. The authors identified an association of Bifidobacterium with the antitumor effects. Further, oral delivery of Bifidobacterium decreased tumor growth with a similar degree as PD-L1 antibody therapy [19]. Importantly, coadministration of the PD-L1 antibody with Bifidobacterium showed a significant reduction in tumor growth by activating the intratumoral and splenic dendritic cells (DCs) [19]. A melanoma study identified a 38% response rate to PD-L1 blockade therapy [20]. Responders and non-responders harbor 10 different bacterial species including *Bifidobacterium*. When fecal material transferred from responders and non-responders into the tumor-bearing mice, the mice with responder's fecal material showed reduced tumor growth. Importantly, the PD-L1 blockade therapy showed its antitumor effects in mice colonized with the responder's bacteria, whereas the therapy was ineffective in the mice having non-responders bacteria [20]. Primary resistance to PD-1/PD-L1 checkpoint inhibitor therapy is suggested to associate with the abnormal gut microbiome composition [21]. The use of antibiotics inhibits the clinical benefit of PD-1/PD-L1 therapy in patients with advanced cancer [21]. The antitumor efficacy of CTLA-4 blockade was shown to be partly dependent on distinct *Bacteroides* species which is a common human colonic flora [22]. In cancer patients and tumor-bearing mice, *Bacteroides fragilis* influenced the outcome of CTLA-4 blockade by inducing the T cell responses. Interestingly, antibiotic-treated or germ-free mice did not show any response to CTLA-4 inhibitor, however, this defect was restored after oral gavage or immunization with *Bacteroides fragilis* polysaccharides [22].

The activity of the gut microbiota affects human health and has been associated with the response of checkpoint inhibitor anticancer immunotherapies. The regulation of microbiota and/or application of fecal microbiota transplantation as a supportive therapy also showed its potential in improved efficacy of immunotherapy. Gut microbiota augments the antigen presentation capability of DCs that promote the recruitment of CD4+ memory T-cells from mesenteric and draining lymph nodes to the tumor microenvironment leading to the trafficking and activation of effector T-cells that induce antitumor immune response. Despite the insights into the immunomodulatory properties, the underlying mechanism and specific composition of the gut microbiome that favors antitumor immune response are less understood. Efforts in this direction will enable harnessing the maximum potential of the gut microbiome in therapy. Assessment and understanding of the gut microbiota composition as a biomarker in the cancer patient may also help in the prediction of the efficacy of cancer immunotherapy response. However, additional preclinical and clinical studies with a large sample size are necessary to develop gut microbiota as a therapy prediction biomarker. Further, the majority of focus on microbiota and cancer immunotherapy has been given to bacterial species. The role of non-bacterial components including fungi, viruses, and protozoa in the anticancer therapy is yet to investigate. A better understanding of the microbiota function in cancer patients and therapy is crucial for the development of precision medicine.

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