TD2 Precision Oncology

WHITE PAPER

Exploring the Effects of Microbiome in Precision Oncology Therapeutic Development

Background

Precision oncology considers the molecular characteristics of a patient's tumor to determine an ideal approved or investigational therapy that could provide clinical benefit [1]. While prospective profiling of patient's tumors has resulted in improved selection and response to therapies [2–4], this "tumorcentric" approach can fail to account for impact of the complex microenvironment that influences tumor growth and response to therapy. The gut microbiota is a complex ecosystem of microorganisms. These microbes play fundamental roles in health and survival and have been found to play a significant role in the response to cancer therapy and susceptibility to toxic side effects of those drugs [5-6].

Effects of SCFA

Through fermentation of carbohydrates that escape absorption in the small intestine, gut microbiota generates short chain fatty acids (SCFA) [7]. SCFA have a wide range of activity and have been reported to actively metabolize more than 40 drugs, including several anti-cancer drugs. [9]

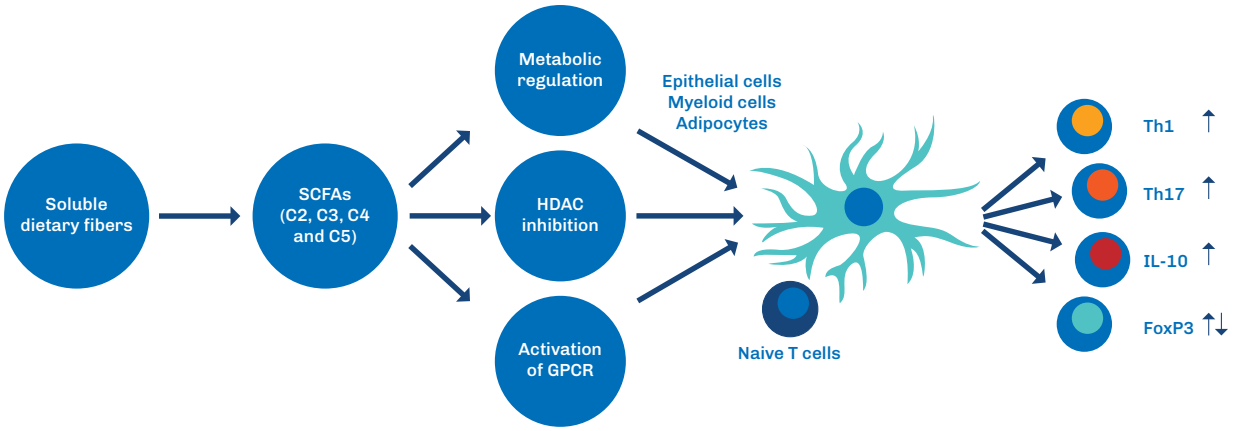
The major SCFA products produced are formate, acetate, propionate, and butyrate. SCFAs are reported to directly activate G-coupled receptors, inhibit histone deacetylases (HDACs), serve as energy substrates, and promote T-cell differentiation into both effector and regulatory T cells to promote either immunity or immune tolerance [7-8].

Role of microbiome in drug metabolism

Gut microbiota may also directly or indirectly increase the metabolism of orally and systemically delivered drugs through SCFA modulation of cytochrome P450 (Cyp450) gene family members [12-14]. Germ-free mice demonstrate faster metabolism of many drugs suggesting the microbiota and SCFAs exert regulatory control over the rate of drug metabolism and detoxification [12]. The heterogeneity of clinical response to drug therapy and/or variable emergence of toxicities may be due in part to differences in gut microbiota composition and differential drug metabolism [15].

Implications for immunotherapy development

Recent literature suggests gut microbiota play an important role in checkpoint inhibitor activity. The anti-tumor activity of anti-PD-1 alone or when combined with anti-CTLA4 was significantly decreased when mice were treated with a broad-spectrum antibiotic combination (ampicillin + colistin + streptomycin) [16]. This experimental data was then confirmed and extended to patients with advanced NSCLC, RCC, or urothelial carcinoma (n = 42) who received PD-1/PD-L1



monoclonal antibodies. Broad spectrum antibiotic treatment in these patients resulted in resistance to PD-1 blockade [16]. Metagenomic analysis of patient stool samples revealed correlations between clinical response to checkpoint inhibitors and the relative abundance of Akkermansia muciniphila, and in preclinical studies supplementation with A. muciniphila restored the efficacy of PD-1 blockade [16]. More recently fecal microbiota transplant was found to induce response to anti-PD1 therapy in patients with melanoma previously shown to be immunotherapy-refractory [17].

Improving preclinical drug development by limiting variability

The murine microbiome can impact early-stage preclinical immuno-oncology studies, so it is critical to include an assessment on the stability of the microbiome to improve study outcome and reproducibility [18]. Ensuring a consistent vendor for experimental animals, feed, and holding rooms are some of the critical factors that could contribute to consistent, and reliable study outcomes.

Future Considerations

The variability in gut microbiota found in patients results in heterogeneous response to therapeutic interventions. Cancer patients are taking a variety of prescription and over-the-counter concomitant medications, all of which can alter the composition of the gut microbiota.

Because cancer patients are already closely monitored when participating in clinical trials it will be important to add comprehensive microbiome assessments, including metaproteomic assessments to treatment protocols to fully understand baseline microbiota in cancer patients and to study the impact of therapies on specific bacterial taxa and their contribution to therapeutic outcomes.

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