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From Gut Microbial Metabolites to T-Cell Immunity: Short-Chain Fatty Acids in PD-1 Inhibitor Response

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Abstract. Microbial metabolites are one route through which the gut microbiota may influence host immune responses, and short-chain fatty acids (SCFAs) have been widely studied for their potential roles in immune regulation. SCFAs can affect T cells through receptor signaling, histone deacetylase inhibition, and metabolic regulation, and may influence both $CD8^+$ effector T cells and regulatory T cells. Clinical studies have reported that SCFA-related microbial features are associated with responses to (protein 1) PD-1 based treatment, while separate studies using direct metabolite measurements have also linked fecal or circulating SCFA levels with treatment outcomes. However, these findings remain mainly observation. The effects of SCFAs also differ according to metabolite type and concentration, tissue compartment, tumor type, treatment setting, and host microbiome background. Therefore, although SCFAs can connect the metabolic functions of the gut microbiota with T cell-mediated anti-tumor immunity, the exact way they induce the effect of PD-1 inhibitors is not yet known. Although the two are good supplements to the regulation of the gut microbiota, more prospective and intervention studies need to be conducted before they can be used clinically.

Keywords: Gut microbiota, Microbial metabolites, Short-chain fatty acids, T-cell immunity, PD-1 inhibitors

1. Introduction

Immune checkpoint inhibitors are now widely used in the treatment of cancer to restore the body's anti-cancer immune system in some patients. Among these therapies, programmed cell death PD-1 inhibitors prevent inhibitory signals that limit the function of T cells. However, the patterns of resistance to PD-1 blockade in patients vary. Some patients are initially non-responders and do not respond to treatment at first; others respond to treatment initially but then develop resistance later on. Different responses to treatment have led to research exploring the reasons behind the different effects of PD-1 inhibitors.

Recently, research on other reasons for this has also focused on the gut microbiota. The gut microbiota can modulate the host immune system and thus affect the immune system at all levels [1]. Clinical studies have shown that differences in the gut microbiota of various cancers are associated with different responses to PD-1/PD-L1 inhibitors [2]. Only the difference in bacterial composition cannot fully explain the observed effects; we do not know what biological functions are

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carried out by these microorganisms. One way in which the gut microbiota can affect the immune system of the host is by producing microbial metabolites that interact with immune cells and deliver functional signals to the host from the gut microbiota [1, 3].

Among the microbially produced metabolites, SCFAs have gained considerable attention due to their close relationship with diet, microbial metabolism and immune regulation. Microbial fermentation in the gut produces several SCFAs, and acetate, propionate and butyrate are the three main kinds [4]. Environmental factors, diet and antibiotic exposure are likely to alter the structure and function of the gut microbiome; thus, the production of SCFAs in the intestine may be reduced [4]. SCFAs can modulate both the regulation and the effect of regulatory T cells, so they may also help to regulate immune activation and immune suppression [4, 5]. This is particularly true for cancer immunotherapy, where the effectiveness of anti-cancer T-cell activation in treating cancer is also affected by regulatory and suppressive immune mechanisms.

Clinical evidence has started to link SCFA profiles with the results of PD-1-targeted therapy. Some patients with a good response to treatment or a longer progression-free survival had higher levels of certain SCFAs in their stool or blood. However, these results are based on observation, and the effect of SCFAs may vary among individuals and conditions. Therefore, it has not been determined whether SCFAs directly enhance the therapeutic effect or function as indicators of an improved gut microbiota.

This paper reviews the role of SCFAs as a possible connection between gut microbial metabolism and T cell immunity in the context of PD-1 inhibitor therapy. First, it introduces the association among SCFAs and T-cell function, then investigates clinical data related to SCFA-related attributes and PD-1 inhibitor responses. The study will also determine whether these effects vary among individuals with different biological characteristics and treatment statuses, and if modification of the gut microbiota could be employed in conjunction with cancer immunotherapy.

2. Gut microbial metabolites

2.1. Linking the microbiota to T cell immunity

The gut microbiota can affect host immunity through multiple mechanisms. Among these mechanisms, the production of microbial metabolites provides an important link between the gut microbiota and T cell immunity [1]. This effect of gut microbiota is not only determined by which bacteria are present, but also related to the metabolites produced by these bacteria. Metabolites produced by the gut microbiota, such as SCFAs and secondary bile acids, can regulate biological behavior of T cells [3].

Among these metabolites, SCFAs mainly consist of acetate, propionate and butyrate. They are mainly produced when intestinal bacteria ferment carbohydrates that can be utilized by microorganisms in the colon [1, 4]. In addition to regulating mucosal immunity, SCFAs derived from the intestine can also exert immune regulatory effects outside the intestine. This provides a potential mechanism through which microbial metabolism may influence systemic immunity [4].

T cells are important immune-cell targets of microbial metabolites. Gut-derived metabolites can affect how T cell develop, become activated, and carry out their functions [3]. In experimental models, butyrate has been reported to support the development of peripheral regulatory T cells [4]. SCFAs can also modulate the functions of both regulatory T cells and effector T cells [3]. These studies indicate that SCFAs may act as functional intermediates between the gut microbiota and T cell immunity. This link is also relevant to cancer immunotherapy, in which effective antitumor responses depend strongly on T cell activity.

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2.2. SCFAs and T cell function

SCFAs can regulate T cell functions through various mechanisms. One proposed mechanism involves G protein-coupled receptor signaling, including receptors such as FFAR2/GPR43 and FFAR3/GPR41 [4]. However, the effects of SCFAs can differ between metabolites, cell types and tissue environments. Another mechanism is related to HDAC inhibition. Butyrate and Propionate can inhibit HDAC activity and promote the generation of peripheral Treg cells [5]. SCFAs can also alter the metabolism of cells and affect how T cells obtain energy to maintain their functions [4]. SCFAs can alter the proportion of various T-cell subtypes and, in particular, the $CD8^+$ T cells that support anti-tumor immunity.

Bachem et al. found that exposure to butyrate is associated with metabolic reprogramming in activated $CD8^+$ T cells and supports their subsequent differentiation into memory cells [6]. Butyrate can help $CD8^+$ T cells prolong the expression of memory genes after antigen stimulation. Zhu and others also found that butyrate enhances the T-cell receptor signalisation of $CD8^+$ cytotoxic lymphocytes and promotes the production of anti-tumour cytokines such as IFN-γ and TNF-α [7]. In tumor-bearing mice, the effect of combining butyrate and anti-PD-1 therapy was significantly reduced after the elimination of $CD8^+$ T cells [7]. Based on the above preclinical results, $CD8^+$ T cell activity may be involved in the anti-tumour effect of butyrate in combination with anti-PD-1 therapy. However, it is unknown if the same mechanism exists in these patients. Together, these results provide a possible preclinical explanation for how butyrate may affect the function of $CD8^+$ T cells during anti-PD-1 treatment.

SCFAs can also modulate $CD4^+$ regulatory T cells (Tregs). Butyrate and Propionate have also been shown to promote the generation of peripheral Tregs through HDAC inhibition [4, 5]. Therefore, SCFAs can modulate T-cell responses by either promoting or suppressing effector functions. The general immune effects of SCFAs may vary according to the type and concentration of SCFAs, the T-cell subset involved, the tumour type, the tissue compartment, and the context of immune checkpoint inhibition. Therefore, the effect of these is neither purely stimulating nor inhibiting. The two are required for effective anti-cancer immunotherapy; otherwise, there will be either insufficient tumour-killing effects or adverse regulatory effects by the immune system. Therefore, it is necessary to determine whether the changes in SCFA are different among patients with various responses to PD-1 blockade.

3. SCFAs and PD-1 inhibitor response

3.1. Microbiota and SCFAs associated with PD-1 responses

Clinical evidence indicates that the composition and metabolic function of the gut microbiota may differ according to how patients respond to PD-1/PD-L1 inhibitors. Peng et al. analyzed gut microbial profiles in a cohort of 74 individuals with advanced gastrointestinal cancer receiving PD-1/PD-L1 blockade [2]. The study found differences in gut microbial composition among patients with different treatment responses, suggesting that the intestinal microbial environment may be related to immunotherapy outcomes [2]. Metagenomic analysis further showed differences in microbial functional pathways between response groups, including pathways related to fermentation and potential SCFA-producing capacity [2]. However, these pathway differences indicate metabolic potential rather than directly measured SCFA production or concentration. Some bacteria with the ability to produce SCFAs were also more strongly associated with favorable treatment response [2].

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The observed associations point to a possible role for microbial function, in addition to bacterial composition, in shaping responses to PD-1/PD-L1 therapy. However, the presence of SCFAs-producing bacteria or SCFAs-related pathways does not directly show that patients have higher SCFA concentrations. And it does not prove that SCFAs themselves improve treatment response. Therefore, direct measurement of SCFA levels is needed to further examine their relationship with clinical outcomes.

3.2. SCFA levels and clinical outcomes

Direct measurement of SCFAs provides more specific information about metabolite exposure and its association with PD-1 inhibitor outcomes, although it does not by itself establish that SCFAs improve treatment efficacy. Nomura et al. Prospectively evaluated 52 patients with solid tumors who received nivolumab or pembrolizumab [8]. The study reported an overall response rate of 28.8%. Patients with higher fecal concentrations of acetate, propionate, butyrate, and valerate also tended to have longer progression-free survival (PFS) [8]. In multivariable analysis, fecal propionate continued to show a significant relationship with PFS (HR 0.07, 95% CI 0.03-0.19) [8]. These finding suggest that some individual SCFAs may be more closely related to treatment outcome than the overall amount of SCFAs.

Another notable result was the lack of a significant correlation between fecal and plasma levels of individual SCFAs [8]. Fecal SCFAs mainly reflect microbial production and use within the intestine, while circulating SCFAs are influenced by intestinal absorption and host metabolism. Therefore, measurements from different biological samples may represent different conditions and should not be treated as the same type of marker.

A similar association was reported by Zhu et al. in a group of individuals receiving anti-PD-1-based therapy for non-small cell lung cancer. Among 22 patients, responders had higher serum levels of acetate, propionate and butyrate than non-responders [7]. Higher serum butyrate levels were associated with greater PD-1 levels in circulating $CD8^+$ T cells [7]. However, the biological meaning of this association remains uncertain, because increased PD-1 expression can be observed in both activated and exhausted T cell states and therefore requires additional phenotypic and functional evidence for interpretation. Taken together, these studies show that SCFA profiles are associated with responses to PD-1-based treatment. However, the patient groups were relatively small and the studies were mainly observational. It is therefore still unclear whether SCFAs directly contribute to treatment efficacy or whether they mainly reflect a gut microbial environment that is already favorable for antitumor immunity.

3.3. Context-dependent effects and evidence gaps

Although several studies have reported favorable associations between SCFAs and PD-1 inhibitor outcomes, the effects of SCFAs do not appear to be consistently beneficial during immune checkpoint therapy. Coutzac et al. showed that patients with higher systemic butyrate and propionate levels showed a weaker response to CTLA-4 blockade and had more regulatory T cells [9]. In mouse models, butyrate was linked to weaker dendritic-cell stimulation and lower numbers of tumor-specific and memory T cells during anti-CTLA-4 treatment [9].

These findings differ from the favorable associations reported in studies of PD-1-based treatment [7, 8]. However, the studies were conducted in different treatment and biological settings. Important different include the immune checkpoint being targeted, SCFA type and concentration, biological compartment, cancer type, treatment regimen, and host microbiome background. The above factors

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can affect the extent of SCFA exposure and the immune cell population involved in tumour immunity. Therefore, the same SCFA may not have the same effect in all clinical situations. In addition, the patient groups of available clinical trials are generally small and heterogeneous, and most provide only associative, rather than causal, evidence. Thus, according to the current evidence, SCFAs and immune checkpoint inhibitors have a context-dependent relationship. However, it has not been demonstrated that SCFAs directly alter the response to treatment, and they have not been identified as effective biomarkers or therapeutic targets.

4. Gut microbiota modulation as an adjuvant strategy

One way to modify the gut microbial environment for cancer immunotherapy is through dietary intervention. Dietary fibre is a substrate for microbial fermentation and thus may affect the production of SCFAs. Spencer et al. investigated the diet of patients with melanoma treated by immune-checkpoint inhibitors and found that those who ate more fibre lived longer without recurrence [10]. Association was strongest among patients who reported sufficient dietary fibre intake and did not use probiotics [10]. Based on the above analysis, diet can affect immunotherapy through changes in the gut microbiota; however, the specific role of SCFAs is still unknown.

Fecal microbiota transplantation (FMT) is a way to alter the gut microbial population more directly. Davar and his colleagues examined the effect of FMT in patients with melanoma who had previously failed PD-1 blockade by combining anti-PD-1 treatment with FMT [11]. Clinical benefits were observed in 6 of the 15 patients [11]. The responsive group also showed an improvement in gut microbial composition and increased $CD8^+$ T cell activation [11]. The above results are early clinical indications that modifications to the gut microbiota may help some patients regain response to PD-1 inhibitors. FMT alters the entire range of bacteria and their metabolic pathways; therefore, the observed effect may not be solely due to SCFAs.

Therefore, the current evidence does not support the application of microbiota modification in combination with PD-1 inhibitors. Important challenges include differences in the microbiome between individuals, donor selection, safety and the lack of standardized intervention methods. In addition, the particular contribution of SCFAs is unknown. An increase in the total production of SCFA may not be appropriate; otherwise, the immune effect could change due to biological or treatment reasons. Future studies will combine microbiome composition and metabolite levels with T-cell response data and clinical outcomes to identify specific microbiota-SCFA profiles that can predict the efficacy of PD-1 inhibitors. Separate intervention studies are also required to determine whether modification of the gut microbiota or SCFA-related pathways can improve the treatment effect.

5. Conclusion

Microbial metabolites are one way through which gut bacteria can influence host immune responses, and SCFAs have been widely studied in this context. Current evidence shows that SCFAs can influence T cell function through several mechanisms and may affect both $CD8^+$ effector T cells and regulatory T cells. These different effects suggest that the immune activity of SCFAs is context-denouement, as different SCFAs, concentrations, and immune-cell populations may produce different outcomes under different biological and treatment conditions.

Clinical studies have reported associations between SCFA-related microbial features, measured SCFA levels, and outcomes of PD-1-based treatment. However, most available evidence remains observational, and it is still unclear whether SCFAs directly improve treatment response or mainly

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reflect a gut microbial environment that is favorable for antitumor immunity. Differences in SCFA type and concentration, cancer type, biological compartment, treatment regimen, and host microbiome background may also contribute to the variation between studies.

Dietary intervention or fecal microbiota transplantation may offer a possible way to support cancer immunotherapy, but current evidence is not sufficient for routine clinical use. Future studies should separately determine whether microbiota-SCFA profiles can serve as predictive biomarkers and whether targeted modification of this pathway can improve PD-1 inhibitor efficacy.

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