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REVIEW ARTICLE

Intestinal Microbiota Associated With The Efficacy Of Immune Checkpoint Inhibitor Therapy With Anti-Pd-1/ Pd-L1 Antibody

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Abstract

We explained about reports of fecal bacteria that could be biomarkers related to the efficacy of immune checkpoint inhibitor therapy with anti-PD-1/PD-L1 antibody against melanoma, non-small cell lung carcinoma (NSCLC), urothelial and renal cell carcinoma (UTC/RCC). It has been reported that the proportion of bacteria in the family *Ruminococcaseae* and *Faecalibacterium* affects the efficacy of immune checkpoint inhibitor therapy as biomarkers against melanoma, and *Akkermansia muchiniphila* as a biomarker against NSCLC and UTC/RCC. However, it is unlikely that these intestinal bacteria can be applied to all carcinomas, and the mechanism of antitumor effects in these bacteria has not yet been fully elucidated.

Introduction

Conventional standard therapies for cancer treatments are surgical treatments, chemotherapies, and radiotherapies. The immune checkpoint inhibitor treatment has rapidly developed and attracted attention as a fourth cancer treatment method in recent years. Immune checkpoint inhibitors exert therapeutic effects by destroying the immunosuppressive environment of cancer, which contributes to treatment resistance. It is an innovative treatment which has never been seen before, but there are challenges which must be overcome. The most urgent issue to overcome is the identification of biomarkers which predict clinical effects and adverse events. Most reports of biomarkers were so far are judged at the molecular and cellular levels, but in recent years, with the development of high-throughput genetic diagnosis analysis systems such as next-generation sequencers, cancer-related genes of individual patients have been developed. And now, research on the development of biomarkers focusing on the intestinal microbiota has begun. We describe the progress, challenges and prospects of intestinal microbiota research which correlates with the current status and therapeutic effects of immune checkpoint inhibitors against cancer in this review.

Current status of biomarkers related to clinical effects of immune checkpoint inhibitors

For living organisms, cytotoxic T-lymphocyte associated protein 4 (CTLA-4, CD152), programmed death 1 (CD279) / programmed death-ligand 1, CD274 (PD-1 / PDL-1), PDL-2 (CD273) [1-3]. It is provided with a group of immunosuppressive co-signaling molecules called representative immune checkpoint molecules. Originally, the immune checkpoint molecule group functions to prevent excessive activation and runaway of the immune system by inducing expression at appropriate cells / sites at appropriate timing. It is known that immune checkpoint molecules are abnormally highly expressed in the tumor microenvironment [4-6]. Therefore, a strong immunosuppressive environment is formed in cancer tissues, which is a major factor in treatment resistance in many carcinomas. The immune checkpoint inhibitor therapy is a treatment method aimed at releasing or alleviating the immunosuppressive mechanism in tumor microenvironments against such an immune escape mechanism [7]. So far, the response rate of immune checkpoint inhibitors alone has been estimated to be about 10-40% [8-12].

Biomarkers which predict its efficacy / ineffectiveness have been reported as biomarkers which are judged at the cellular and molecular levels [13-16]. For detailed, it has been proposed as biomarkers that the infiltration of T cells into or around cancer tissues, in the connection with immune checkpoint inhibitor therapy using anti-PD-1and anti-PD-L1 antibodies against multiple carcinomas such as melanoma. And, it has been also proposed that the formation of B cell-rich cell aggregates in cancer tissues, the expression of PD-L1 on cancer cells and the

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expression of PD-L1 on immune cells infiltrating cancer tissues are judged at the cellular and molecular levels. Even though, problems such as spatiotemporal fluctuations and ambiguity in cutoff values have been pointed out for these biomarkers [8, 17-22]. On the other hand, with the spread of gene analysis technology such as next-generation sequencers and advances in bioinformatics, there have been many reports of finding biomarkers from genetic information of cancer cells and immune cells [23-29]. To date, biomarkers found in the genetic information of cancer cells has been reported gene biomarkers such as mismatch repair gene deficiency or dysfunction, high-frequency microsatellite instability, abundance of oscillating antigens associated with gene mutations, and Wnt / β catenin signaling pathway. Biomarkers found from genetic information of immune cells has been reported gene biomarkers such as T cell receptor repertoire diversity of peripheral blood T cells and T cell receptor repertoire diversity of T cells infiltrated into tumor cells.

However, depending on the type of carcinoma, it may be difficult to collect samples such as biopsies. Moreover, biomarkers reported so far have not been correlated in all carcinomas. Therefore, a new approach is required to establish effective biomarkers for treatment selection for each patient. In recent years, an attention has been focused on the analysis of intestinal microbiota for patients with carcinoma using feces, which is easier to collect than biopsies.

Development of biomarkers targeting the intestinal microbiota

This review describes biomarkers targeting intestinal microbiota which affect cancer immunotherapies with immune checkpoint-inhibiting antibodies, especially anti-PD-1 / PD-L1 antibody. Recent studies have reported that intestinal microbiota affects the host's immune system and is closely associated with diseases such as autoimmune disorders [30-32]. Based on above findings, studies focusing on the relationship between the efficacy / ineffectiveness of immune checkpoint inhibitors and intestinal microbiota have been conducted. Intestinal bacteria as biomarkers which relate to the therapeutic effect of immune checkpoint inhibitors using PD-L1 antibody in addition to anti-PD-1 antibody has been revealed in melanoma, and other carcinomas [33].

Intestinal microbiota as a biomarker for melanoma

The effect of intestinal bacteria on the efficacy of immune checkpoint inhibitor targeting PD-1 / PD-L1 has been first reported in a mice melanoma model [34]. According to this report, tumor growth was suppressed the group which bacteria of the genus *Bifidobacterium* (including *Bifidobacterium breve*, *Bifidobacterium longum*) was orally administered to model mice, and the antitumor effect was enhanced by the combined use of anti-PD-L1 antibody. Tumor-specific T cells were increased in tumor tissue and peripheral blood in mice with antitumor effects, but antitumor effects were not observed in the group which CD8-positive T cells were removed by anti-CD8 antibody administration. Furthermore, when dendritic cells after administration of bacteria of the genus of *Bifidobacterium* were analyzed, the ability to induce antigen presentation / activation for CD8-positive T cells was enhanced. This report stated that antitumor effects after administration of bacteria of the genus *Bifidobacterium* were due to the induction of T cell immunity through activation of dendritic cells, rather than bacteria affect directly on cancer cells [34]. And, this report also stated that antitumor effects were not observed when administered heat-treated inactivated bacteria of the genus *Bifidobacterium*. Innate immune systems, including Toll-like receptors, are generally involved in the activation of dendritic cells by bacteria, but this report shows that administered bacteria need to colonize the host's intestine in order to activate dendritic cells. It suggests that administration of bacterial components alone is not effective [34]. Several bacteria of the genus *Bifidobacterium* have been reported to directly activate dendritic cells and affect immune responses of host T cells [35- 39]. Specifically, cell wall components of the eight bacterial strains in the probiotic preparation VSL#3 (four lactobacilli, three bifidobacteria and one streptococcal strains), cell surface components obtained by sonication of *Bifidobacterium longum* strains, commensal bacteria and different strains of *Bifidobacterium* have been reported. In short, these bacteria do not exert direct antitumor actions, but dendritic cells activated by these bacteria exert antitumor effects by inducing CD8-positive T cells with antitumor actions. To dendritic cells activation which holds the key to antitumor activity, it is essential that these bacteria to colonize the host's intestine.

Next then, a cohort study based on the results of the above mice model has been reported. It was a report of collecting fecal samples before anti-PD-1 antibody treatment in patients with metastatic melanoma to examine the composition of intestinal microbiota and the subsequent therapeutic effect. The results showed that the proportion of 8 species of bacteria, including *Bifidobacterium longum*, *Collinsella arerofaciens*, and *Enterococcus faecium*, was higher than that of the non-responders' patients who responded to the treatment with feces [40]. And, *Ruminococcus obeum* and *Roseburia intestinalis* had a higher proportion of these bacterial species in feces of non-responders than those of responders [40]. Furthermore, in this report, when sterile mice were orally administered with responders' or non-responders' feces and then inoculated with melanoma cells, remarkable antitumor effects were observed only in the group inoculated with responders' feces. In this mice model, tumor-specific T cells were increased not only in the spleen but also in the tumor tissue [40]. These results indicate that some intestinal bacteria derived from responders formed

colonies in the intestinal tract of mice to induce a tumor-specific immune response. Based on above results, this cohort study reported that intestinal bacteria including *Bifidobacterium longum* may be potential biomarkers for estimating the therapeutic effect of immune checkpoint inhibitors using anti-PD-L1 antibody therapy against melanoma [40].

On the other hand, there was a group reporting a cohort study different from the above.

They also collected and analyzed fecal samples before and after anti-PD-L1 antibody therapy from patients with metastatic melanoma, reported that responders' feces were high diversity in fecal bacteria than non-responders' feces. And, they also found that the group with high diversity of fecal bacteria had significantly longer progression-free survival (PFS) than the group with low diversity. As results, it was clarified that the diversity of fecal microbiota in responders' feces was more pronounced than those non-responders, and the progression-free survival (PFS) was also significantly longer in the group with high diversity of fecal microbiota [41]. In this report, feces of responders were rich in bacteria of the family *Ruminococcaseae*, and feces of non-responders were rich in bacteria of the order *Bacteroidales*. Moreover, it was reported that PFS was significantly shorter in the group with a high proportion of *Faecalibacterium* in the family *Ruminococcaseae* than in the group with a low proportion [41]. Additionally, they collected tumor tissues and performed immunohistochemical analysis, and they reported that there was the positive correlation between infiltration of CD8-positive T cells into tumor cells and bacteria of the family *Ruminococcaseae*, bacteria of the genus *Faecalibacterium*. Conversely, they have reported that bacteria of the order *Bacteroidales* tendency to show the negative correlation for them [41]. In addition, they performed the analysis of immune cells in peripheral blood to examine systemic immune responses and analyzed antitumor T cells such as CD8-positive T cells and effector CD4-positive T cells in a high proportion of bacteria of the family *Ruminococcaseae* and *Faecalibacterium*. And conversely, they have also reported the increase of immunosuppressive cells such as regulatory T cells (Tregs) in the group with a high proportion of *Bacteroidales* [41]. Furthermore, they confirmed that the significant antitumor effect was observed only in the group inoculated with responder feces when sterile mice were orally administered with responder or non-responder feces and then inoculated with melanoma cells. In mice with remarkable antitumor effects, tumor-specific T cells were increased not only in spleen but also in tumor tissues [41]. This result indicates that responder-derived bacteria colonized the mice intestine and formed a tumor microenvironment with significant T cell infiltration.

Moreover, it has been reported that not only CD8-positive T cells but also effector cells expressing CD45, CD11b, and Ly6G are increased in tumor tissues of mice which responders' feces were administered [42]. There was a report that the number of immunosuppressive cells expressing CD11b and CD11c decreases [43]. Alternatively, there was also a report that spleen of mice treated with non-responders' feces showed the increase of Treg compared to the group treated with responders' feces [40]. These results indicate that specific intestinal bacteria administered must colonize mice intestinal tract in order to affect the antitumor immunity. This is consistent with the results of the above cohort study.

From these research reports, it indicated that the ratio of bacteria of the family *Ruminococcaseae* and the genus *Faecalibacterium* in feces related the efficacy of immune checkpoint inhibitor using anti-PD-L1 antibody against melanoma, and bacteria of the order *Bacteroidales* correlates with ineffectiveness [40].

Intestinal microbiota as a biomarker for non-small-cell lung carcinoma, urothelial and renal cell carcinoma

For carcinomas other than melanoma, the cohort study of patients with non-small cell lung carcinoma (NSCLC), urothelial and renal cell carcinoma (UTC / RCC) has been reported [44]. This is to verify the correlation between the presence or absence of antibiotic administration and the efficacy of immune checkpoint inhibitors by anti-PD-1 / PD-L1 antibody. To outline this cohort, patients who did not receive antibiotics before and after administration of anti-PD-1 / PD-L1 antibody had longer PFS and overall survival compared to those who received antibiotics. This is similar to the experimental mice cancer-bearing model study, and indicates that the decrease in intestinal bacteria and the change in composition affected the effect of anti-PD-1/ PD-L1 antibody therapy by administration of antibiotics. They analyzed the microbial flora using fecal samples in patients with NSCLS and UTC / RCC on above results, and reported that *Akkermansia muchiniphila* (A. muchiniphila) showed the strongest correlation with the efficacy of anti-PD-1 / PD-L1 antibody therapy [44]. This report shows that when CD4 + T cells and CD8 + T cells collected from the patient's peripheral blood are reacted with A. muchiniphila, there is a positive correlation between the IFN-γ produced from those T cells and the duration of PFS. This is very interesting findings, and suggests that *A. muchiniphila* may specifically promote T cell-responsive tumor immunity systemically. In addition, they examined the oral administration of responders' or non-responders' patients feces to sterile mice or mice administered with antibiotics to inoculate tumor cells, and then to perform anti-PD-L1 antibody therapy. As results, a remarkable antitumor effect was observed only in the group to which responders' feces was administered, and infiltration of CD4 positive T cells having a high antitumor effect was remarkable in tumor tissues of the mice group which responders' feces

were administered. More notably, they found that additional administration of *A. muchiniphila* to the group of mice orally administered with non-responder's patient feces restored the therapeutic effect of anti-PD-L1 antibody. They have reported that this effect may be due to a decrease in Treg cells and an increase in helper T1 cell (Th1) by immunohistochemistry [44]. Tumor tissues are generally immunosuppressed state. However, this report suggests that the combined use of *A. muchiniphila* and anti-PD-L1 antibody therapy induces an immunostimulatory state in tumor tissues. Furthermore, it has been reported that stimulation of dendritic cells with *A. muchiniphila* in vivo produces IL-12, which acts on Th1 cell differentiation. In this report, non-responders' feces were intraperitoneally administered to mice with anti-IL-12 antibody or anti-INF antibody to neutralize the action of cytokines, respectively. And, they have confirmed that the antitumor effect had disappeared, and stated that induction of Th1 cells was important for *A. muchiniphila* and anti-PD-L1 antibody therapy [45].

From these research reports, it is considered that the efficacy of anti-PD-1 / PD-L1 antibody is affected by inducing Th1 cell differentiation triggered by colonization in the intestinal tract of *A. muchiniphila*. Therefore, it is suggested that *A. muchiniphila* may be used as a biomarker for immune checkpoint inhibitor therapy using anti-PD-1 / PD-L1 antibody for patients with NSCLC and UTC / RCC, and clinical development is expected in future.

Problems with intestinal microbiota as a biomarker for predicting effects of immune checkpoint inhibitor therapy

There are many unclear problems about the mechanism which specific intestinal bacteria mentioned in this review affect antitumor effects. The first question is whether reported special bacteria have special components or secretions which are not present in other bacteria. The second question is whether reported special bacteria have T-cell epitopes similar to tumor-related antigens and newborn cancer antigens, but induce cross-reactivity to tumors. The third question is the question of bacterial differences in ethnicity, eating habits and living environment in each cohort study. The fourth question is special bacteria colonize in intestine, but how control the immune response against tumors which are distant from intestine. I would like to mention that above problems must be clarified in future in order for specific intestinal bacteria and their derivatives as probiotics, to become new candidates for combination therapy using immune checkpoint inhibitors.

Conclusions, prospects and challenges

This review focuses on intestinal bacteria that may be biomarkers that correlate with the efficacy of immune checkpoint inhibitor therapy with anti-PD-1 / PD-L1 antibody. In addition to reports described this time, retrospective cohort studies using various clinical specimens and feces are currently underway. Unfortunately, it is unlikely that the intestinal bacteria described this time will be universally applicable to all carcinomas and all cases. It will be necessary to comprehensively analyze and integrate multiple biomarkers for each patient after creating a database of patient information with various backgrounds in order to accurately predict therapeutic effects and adverse events in future. It becomes artificial intelligence (AI) will play an increasingly important role in multi-parameter analysis based on this big data.

Also, the mechanism by which the specific intestinal microbiota discussed here affects the antitumor effect has not been fully elucidated [46, 47].

Specific issues include differences in bacterial function / components, tumor specificity, dietary habits and bacterial anti-tumor immune mechanisms. We hope that fecal microbiota transplantation treatment of specific bacteria, and probiotics / prebiotics which induce these bacteria will be used as new combination therapies for the immune checkpoint inhibitor therapy by clarifying the above-mentioned problems in future.

Conflict of Interest

There is no conflict of interest.

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