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REVIEW

Gut Microbiome and Immune Checkpoint Inhibitor-Induced Enterocolitis

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Abstract

The gut microbiome is increasingly being described as one of the underlying mechanisms for development of immune checkpoint inhibitor (ICI)-induced colitis. Similarities in gut microbiome profiles have been found among various diseases associated with intestinal inflammation, including inflammatory bowel disease. Certain bacterial species have been reported to be preventive for colitis, as well as beneficial for cancer outcome, in patients receiving ICI therapy. Alternatively, other bacterial classes have been shown to be associated with immunologic alterations causing intestinal inflammation with subsequent increase in the risk of ICI-related colitis. Gut microbiome manipulation by fecal transplantation has been proposed as one of the modalities to ameliorate inflammation in patients with ICI-related colitis refractory to immunosuppressive therapy. Additional investigations are needed to clarify the role of gut microbiome in the pathogenesis of ICI-related colitis.

Keywords Microbiome · Immune checkpoint inhibitor · Enterocolitis · Colitis · Fecal microbiota transplantation

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Immune checkpoint inhibitors (ICIs) prolong survival of patients with multiple cancer types by targeting programmed death protein-1 or its ligand (PD [L]-1) or cytotoxic T-lymphocyte-associated protein-4 (CTLA-4). Nonetheless, like other effective cancer therapies, ICIs are associated with adverse events that can affect any organ [1]. These adverse events are thought to be immune mediated, especially since ICIs act by boosting the T cell immunity. Gastrointestinal adverse events, particularly enterocolitis, are among the most common and severe immune-mediated adverse events of ICI [2].

Multiple pathogenesis pathways of ICI-induced enterocolitis (IEC) have been proposed. One of the proposed theories is that ICI leads to microbiome dysbiosis [3, 4]. Several reports have recently focused on the gut microbiome and its effect on the development and disease course of IEC, as disturbances of the gut microbiome have been linked to intestinal inflammation [5]. This hypothesis is not surprising, especially since idiopathic inflammatory bowel disease (ulcerative colitis and Crohn's disease) has been linked to microbiome dysbiosis as well, and there is a considerable resemblance between inflammatory bowel disease and IEC [6]. A recent study reported that patients with IBD are at increased risk of IEC [7], supporting the hypothesis that patients with IBD have a microbiome profile that predisposes them to intestinal inflammation. In this review, we narrate the literature on the effect of the gut microbiome and its manipulation on the occurrence and outcome of IEC in patients receiving ICI therapy.

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Several bacteria taxa have been reported to have a distinct impact on IEC, with some inconsistencies among studies. There is some expected overlap between the gut bacteria that was found to cause intestinal inflammation in general and IEC, especially in patients with inflammatory bowel disease. For instance, mirroring what has been reported in IEC, a decrease in abundance of bacteria with phyla *Firmicutes* and *Bacteroides* and an increase in abundance of *Gammaproteobacteria* are among the commonly reported gut microbiome alterations in patients with IBD [8, 9]. This gut perturbation leads to activation of T helper cells 1 and 17, which subsequently result in inflammation of the intestinal mucosa [10]. Furthermore, the activation of T helper cells 1 and 17 allows pathogenic bacteria to stay in the intestines and injure the protective mucus epithelium layer [11].

Chaput et al. [12] reported that *Bacteroidetes* are associated with worse cancer outcome and lower incidence of IEC, and conversely *Faecalibacterium*, in particular *F. prausnitzii* L2-6, butyrate-producing bacterium L2-21 and *G. formicilis* ATCC 27749, are associated with development of IEC and better cancer outcome. Immunologically, the absolute numbers of CD4 T cells are significantly higher in patients who developed ipilimumab-induced colitis compared with patients who did not. In addition, by conducting competing risk analysis on peripheral serum, patients with high numbers of conventional CD4 T cells have a shorter colitis-free interval cumulatively, as opposed to those with low numbers of conventional CD4 T cells. In contrast, patients with IEC have significantly lower levels of IL-6, IL-8, and sCD25 at baseline prior to starting ICI, opposing to those without IEC. The T-regs proportion is lower before the introduction of ipilimumab in patients who developed colitis during ipilimumab treatment course compared with patients who did not develop colitis.

In a case series studying the efficacy of fecal transplant in two patients with IEC, CD8 was predominant at the time of refractory IEC before fecal transplantation, whereas CD4 FoxP3+ proportion expanded after fecal transplant [13]. This finding suggests that CD8 might play a role in the pathogenesis of IEC, and that CD4FoxP3+ might be protective. Moreover, in this study, there was no association between α-diversity and IEC or fecal transplant effect. The gut microbiome of the two patients, immediately after fecal transplant, resembled that of the donor according to the principal coordinate analyses of unweighted unifrac distances. Prior to fecal transplant, the bacteria taxa was different between the two patients and the donor and mainly consisted of *Clostridia* and lacked *Bacteroidia* and *Verrucomicrobiae*, both are bacteria found to be protective from IEC and IBD, respectively [11, 12, 14], in the first patient and consisted of *Escherichia*, a bacteria known to be associated with gut dysbiosis, in the second. Following fecal transplant in the first patient, there was abundance of *Akkermansia*, which later diminished. An expansion of *Bifidobacterium* was also evident after 7 weeks from fecal transplant in the first patient and immediately in the second; this bacterium was found to abrogate the ICI-related toxicities in murine mice and to lessen intestinal inflammation in other report [15, 16].

Dubin et al. [11] studied 34 patients with advanced melanoma and reported that the prevalence of *Bacteroidetes* phylum was associated with resistance to IEC development, attributing this observation to an increase in T-reg cells. The authors concluded that biosynthesis of thiamine, riboflavin, and pantothenate and bacterial polyamine transport system can be used as accurate predictors of risk of IEC in patients receiving CTLA-inhibitors. Limited microbiome diversity correlated with risk of colitis, similar to the reports from IBD as mentioned earlier. A need for further investigation was emphasized in the study to verify their findings.

In another study by Vetizou et al. [17], *Burkholderia cepacia* and *Bacteroides fragilis*, bacteria found to be associated with favorable anti-tumor effect of ICI and to be protective from inflammatory bowel disease, were found to decrease the histopathological inflammation induced by CTLA-4 in the gastrointestinal tract of studied mice, although these mice did not develop symptoms of colitis clinically. Furthermore, *Bifidobacterium*, which has been associated with anti-PD-L1 efficacy in melanoma mouse models [18], along with other bacteria including *Lactobacillus*, has also been demonstrated to be protective against IEC through modulation of cytokine production and strengthening of the gut barrier function [19, 20].

Few reports have studied the effect of the microbiome on ICI and IEC indirectly, by studying the effect of medications that can alter the microbiome, particularly antibiotics which are known to be detrimental to the gut microbiome, on the risk of IEC. Routy et al. [21] investigated the effect of antibiotics on the efficacy of PD-(L)1 inhibitors and found that antibiotics had a deleterious impact on survival by univariate and multivariate analysis. We reported on the impact of antibiotics on IEC in 826 patients at MD Anderson, but did not perform microbiome analysis [22]. Antibiotics, especially with activity against anaerobic bacteria, were linked to more severe IC disease course. This was more prominent when antibiotics were given after starting ICI. Also, survival was shorter among patients who received antibiotics with anaerobic protection.

In conclusion, gut microbiome alteration impacts several inflammatory cascades that can lead to intestinal inflammation in patients receiving ICI therapy. Therefore, manipulation of the gut microbiome by fecal transplantation has been suggested as a method to resolve the inflammation in patients with IEC. Several studies are undergoing to distinguish bacterial classes that may be beneficial in preventing the occurrence of intestinal inflammation from ICI therapy.

Further research efforts are needed to evaluate the use of fecal transplant to prevent IEC recurrence as well, especially that IEC relapsed in a considerable proportion of patients who resumed ICI therapy after IEC [23]. Identifying the bacterial taxa in the microbiome associated with favorable outcomes, both with respect to IEC and cancer, is the ultimate goal. It may be possible to manipulate microbiome composition to prevent complications such as colitis at time of initiating ICI therapy by establishing a beneficial microbiome profile. Further studies are needed to clarify the role of microbiome and its manipulation on IEC.

Key Points

- Gut microbiome dysbiosis leads to a cascade of immunologic changes that can cause intestinal inflammation in a variety of gastrointestinal diseases
- *Bacteroidetes* and *Bifidobacterium* are reported to be associated with lower risk of ICI-related colitis in cancer patients
- *Faecalibacterium, Clostridia,* and *Escherichia* are linked with increased risk of ICI-related colitis
- Gut microbiome manipulation by fecal transplantation can effectively hamper the intestinal inflammation caused by ICI-related colitis

Compliance with Ethical Standards

Conflict of interest YW is a consultant for Tillotts Pharma. HA-S declares no conflict of interest.

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