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GUT MICROBIOTA AND INFLAMMATORY BOWEL DISEASE TREATMENT

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Abstract: The current article is a review of the most important, accessible and relevant literature published between April 2020 and March 2021 on the gut microbiota and inflammatory bowel disease (IBD) treatments. The major areas of publication during this period were human studies involving probiotic supplementation and fecal microbiota transplantation including mechanistic insights from animal models as well as papers covering the more traditional pharmacological IBD treatments.

Keywords: Inflammatory bowel disease, IBD therapeutics, Probiotics, Fecal microbiota transplantation, Microbiome, Microbiota.

PROBIOTICS

Probiotic use in IBD has been the focus of intense debate, with published findings clearly demonstrating that beneficial effects are strain-specific and require sustained consumption to retain efficacy. Four studies[1-4] were published which investigated the potential of candidate probiotic strains in IBD. These included *Lactobacillus rhamnosus* strain LDTM 7511[1], *Lactobacillus casei*[2], *Pediococcus pentosaceus* LI05[3] and *Bifidobacterium bifidum* ATCC 29521[4]. All four studies assessed probiotic efficacy in the dextran sodium sulphate (DSS)-induced murine colitis model, with all strains reducing gut inflammation as well as at least partially restoring microbial dysbiosis. The therapeutic effect of *B. adolescentis* was assessed by Fan et al[5]. Following initial confirmation of reduced levels of *B. adolescentis* in IBD patient stool samples compared with non-IBD controls, mechanistic investigation in a DSS model showed that *B. adolescentis* elicited protective effects including reduced diarrhea scores, spleen weight, and increased colon length. In addition, histopathology inflammatory scores

were reduced in *B. adolescentis* treated animals. In addition, tight junction protein and mucin family were enhanced after *B. adolescentis* treatment and pro-inflammatory cytokine production was reduced whilst anti-inflammatory cytokine levels were increased. The presence of *B. adolescentis* also impacted microbial diversity with an increase in the Bacteroides/Firmicutes ratio whilst limiting excessive growth of *Akkermansia* and *Escherichia-Shigella.* The use of specific microbes, outside of the probiotics space, as novel preventative/therapeutics is also the focus of attention. Zhou et al[6] assessed the impact of monosexual *Schistosoma japonicum cercariae* in reducing the impact of DSS-induced inflammation. Mice treated with DSS and *Schistosoma japonicum cercariae* showed reduced disease symptoms, including less impaired intestinal permeability alongside the development of a modulated Th1/Th2 balance through reduced IFN-γ production, increased IL-10 expression and enhanced Treg subset populations. *Schistosoma* also dramatically reshaped the structure, diversity and richness of the gut microbiota community.

Other studies concerning probiotics evaluation were performed *in vitro*. Using microbiota consortia obtained from 3 UC patients and an *in-vitro* gut system, a study aimed to evaluate the effects of Symprove, a multi-strain probiotic containing *Lactobacillus acidophilus* NCIMB 30175, *Lactobacillus plantarum* NCIMB 30173, *Lactobacillus rhamnosus* NCIMB 30,174 and *Enterococcus faecium* NCIMB 30176[7]. Addition of Symprove changed the bacterial composition over a period of 48 hours. Moreover, production of SCFAs and lactate was induced, with an increase in the production of anti-inflammatory cytokines, while pro-inflammatory cytokines and chemokines decreased. All together, these results confirm that the 4 probiotic strains composing Symprove influences gut microbiota composition and function toward an anti-inflammatory state.

Based on histological changes and gut microbiota analysis, Qingchang Huashi Formula was found to restore gut microbiota-metabolism homeostasis and goblet cells function in a DSS-induced colitis mouse model[8]. In rat, berberine, an alkaloid compound, was found to reduce gut inflammation after DSS. Berberine administration corrects inflammation-induced dysbiosis and prevents gut-barrier dysfunction. A further metabolomic analysis showed that tryptophan catabolites were significantly modulated during colitis, whereas berberine treatment restored tryptophan level back to normal. In addition, the authors performed an *in vitro* mechanistic exploration, which showed that the tryptophan metabolites activated AhR which consequently improved gut barrier function.

In another DSS model, impact of α-tocopherol and γ-tocopherol-rich tocopherols on gut inflammation, gut barrier integrity and microbiota composition was assessed[9]. These two vitamin E forms favourably modified the gut microbial community and showed protective effects on intestinal barrier function. The effect of persimmon-derived tannin was also tested and demonstrated anti-inflammatory properties by impacting the gut microbiota composition and immune response[10]. In another study, the polysaccharide HAW1-2 isolated from *Crataegus pinnatifida* (Hawthorn) directly modified the gut microbiota, leading to the production of SCFAs that inhibited DSS-induced colitis[11]. The anti-inflammatory effects of oligosaccharides from *Periplaneta americana* (OPA) and its possible mechanisms were explored in the DSS model. OPA exhibited anti-inflammatory activity by regulating Th1/Th2 pathways, reducing oxidative stress, and preserving intestinal barrier integrity. Moreover, the protection by OPA was associated with an increase in microbial diversity and beneficial bacteria, and the reduction in pathogenic bacteria in faeces[12]. *Lactobacillus plantarum* mitigated inflammatory colonic lesions, reprogrammed the microbial community and altered the level of serum metabolites in the DSS model[13].

Finally a Cochrane meta-analysis evaluated the randomized controlled trials that compared probiotics with placebo or any other non-probiotic intervention for the induction of remission in Crohn's disease (CD)[14]. Only 2 studies were eligible: one using *Lactobacillus rhamnosus* strain GG and one using freeze-dried *Bifidobacterium longum*. The authors concluded that the efficacy and safety of probiotics, when compared to placebo for induction of remission in CD, is still uncertain. A screen of 29 *L. casei* strains with IBD-alleviating effects based on *in vitro* physiological characteristics was performed. Out of them, five candidate strains were tested in colitis model in mice. Only *Lactobacillus casei* M2S01 effectively relieved colitis and its effect was related to the inhibition of the NF-kB pathway[2]. Another work showed that pre-treatment of mice with *Bifidobacterium bifidum* ATCC 29521 significantly alleviated the

severity of acute colitis on the basis of clinical and pathologic indicators in a DSS-induced colitis mice model[15]. Microbiota analysis showed that pre-treatment with *B. bifidum* ATCC 29521 reduced intestinal inflammation and altered the gut microbiota to favour the genera *Intestinimonas* and *Bacteroides*.

IBD pathogenesis is a complex process, mainly linked to uncontrolled mucosal inflammation which can be triggered by a breakdown in the intestinal homeostasis among the microbiota and resident innate and adaptive immune cells. Concerning, *Lactobacillus* and *Bifidobacterium* strains, a study performed by an Italian team aimed to investigate whether adherent invasive *Escherichia coli* (AIEC) virulence mechanisms interfered with the relative inflammatory response related to the IL-23/Th17 axis in IBD patients[16]. The authors evaluated the specific ability of 2 *Lactobacillus* and 2 *Bifidobacterium* strains to modulate AIEC invasion and survival within intestinal epithelial cells, macrophages and dendritic cells isolated from healthy donors and IBD patients. Probiotic strains were shown to significantly reduce AIEC adhesion and persistence in epithelial cells as well as reducing AIEC survival in immune cells, reducing cytokine levels within the IL-23/Th17 axis in healthy controls and UC patients. However, effects were dramatically reduced in CD patients with only one of the *Bifidobacterium* strains having an effect. The findings highlight the need to consider both probiotic strain potential as well as specific disease-derived immune cells when evaluating novel probiotic strains.

NEW EVIDENCE EXPLORING THE IMPACT OF FECAL MICROBIOTA TRANSPLANTATION IN IBD

Fecal Microbiota Transplantation (FMT) is now extensively explored as a potential therapeutic tool in IBD. Last year one meta-analysis[17], 2 controlled randomized trials[18,19], 6 retrospective[20-24] and 7 prospective uncontrolled studies[25-30] exploring FMT in IBD were published. The vast majority of studies[31,32] involved UC patients, with methodological quality varying between reports. A signal in favour of clinical efficacy in both CD and UC emerged with repeated FMT. However, small number of patients, lack of a control group in most of trials, selection bias and possible confounding factors limited the interpretations that can be made in a number of the studies. In line with these observations a meta-analysis of 36 FMT studies from 2013 to 2020, mostly case series and uncontrolled studies, identified a response rate after FMT of 53.8% with a complete remission of 37% both in UC and CD. In this work, highly limited by the small number of randomized control trials (9 in total), frozen fecal material was associated with better results in terms of clinical remission when compared to fresh material[17]. Interestingly, evaluation of FMT in three small studies of severe UC patients (18 patients in total) did not report the occurrence of severe adverse events while clinical and endoscopic efficacy was described.

RETROSPECTIVE STUDIES

Dang et al[20] published a single centre retrospective systematic case series of 12 patients in China that received multiple FMT for moderate to severe UC. FMT was performed through colonoscopy from either fresh or frozen faeces. A high rate of clinical response defined by an improvement of the SCCAI or UCDAI score of ≥3 was reported (90%; 11/12) at week 52 post-FMT. Five patients achieved remission (SCCAI or UCDAI score ≤2), while no adverse events were described. Patients that relapsed after initial remission did not respond to additional FMT (0/4). The absence of a control group, potential bias in patient selection, imprecision on the exact number of FMT received and concomitant immunomodulatory treatment limited conclusions but interestingly, no adverse event was reported even in the 7 cases of severe UC.

Clinical efficacy for recurrent *C. difficile* (CDI) infection in IBD patients was assessed in two retrospective studies. A small Iranian study reported results of FMT in 8 patients (1 CD, 7 UC) with a primary cure at 6 months of 100% after one or two FMT. Interestingly, 2 patients developed enterotoxin-producing C. *perfringens* infection following FMT, which is an undescribed FMT complication[31]. The second study was performed by Tariq et al[32] and included 145 American IBD patients (53 CD, 89 UC, 3 indeterminate colitis) that had FMT for recurrent CDI. Efficacy regarding CDI without recurrence at 2 months was 80%. IBD therapy escalation after

CDI resolution was performed for 43 patients (29.7%); no de-escalation of IBD therapy was reported. IBD symptoms worsened for 11 patients (7.6%) after FMT, suggesting that CDI exacerbated an existing IBD induced microbiota imbalance while FMT did not change the natural history of the disease for these patients.

UNCONTROLLED PROSPECTIVE STUDIES

Chen and colleagues published a small single-centre prospective open-label trial that assessed short-term efficacy and safety of FMT in moderate or severe UC[25]. Nine patients (6 severe, 3 moderate) with a Mayo score ≥6 and an endoscopic Mayo score ≥2 underwent 3 consecutive FMT (fresh faeces) through nasojejunal tube or transendoscopic enteral tubing at day 1, 3 and 5. Clinical response and clinical remission at week 2 were reported for 7 (77.8%) and 5 (55.6%) patients respectively. At week 12, clinical remission and endoscopic remission were achieved in 6 patients (66.6%) and 3 patients (33.3%) respectively. No severe adverse events were reported. Although all patients were anti-TNFalpha, 5-ASA and steroid naïve, the authors did not define management of IBD therapeutics during the study. However, only 2 patients among those who responded to FMT were on steroids, with one reported as steroid resistant. Of note, enemas of 5-ASA and/or steroids were not allowed.

Another prospective study in Poland reported multi-dose FMT (200 mL) from healthy donors, via colonoscopy/gastroscopy in 10 UC patients. Significant biochemical improvement according to calprotectin fecal levels was described but no evaluation of clinical activity with validated score was reported[26]. A pilot study of sequential FMT to treat CMV (biopsy positive) children with moderate to severe UC was published. Eight children were treated with FMT through nasogastric tube on 5 consecutive days in each of 2 weeks. No antiviral treatment was used, and immunosuppressive therapies were withdrawn. At week 6, CMV PCR on colonic biopsies were negative in 7/8 patients. Clinical response (defined by a decrease of Paediatric UC Activity Index by ≥20 points) was observed in 3/8 patients (37.5%). No adverse events were reported[27].

Lastly, a single-centre, open-label study performed in China assessed the effect of three doses FMT (fresh stool) in 47 patients with mild to moderate UC. The primary endpoint: steroid-free clinical response at week 4 post-FMT was achieved in 84.1% of patients (37/47), and steroid-free clinical remission in 70.5% of patients (31/47). However, mucosal healing (defined by a Mayo endoscopic subscore ≤1) was not achieved in any patient. Clinical efficacy was associated with an increase of *F. prausnitzii,* a bacteria with known anti-inflammatory properties[28].

CONTROLLED RANDOMIZED TRIALS

One controlled open-label randomized trial performed in Hefei in China, assessed the efficacy of a single FMT to treat recurrent mild to severe UC. Primary outcome was defined as steroid-free remission (total Mayo score ≤2 with an endoscopic score ≤1) at week 8. Patients treated with therapies other than 5-ASA and steroids (i.e. biologics, immunosuppressive therapies, surgery) were excluded. Patients received either a single FMT from fresh stool through colonoscopy or a treatment by mesalazine +/- steroids according to disease severity in the control group. Twenty patients were included (10 in each group). Nine patients in the FMT group and 5 patients in the control group achieved the primary outcome at week 8 with Mayo scores significantly lower in the FMT group (p-value=0.019). There was no significant difference in relapse-free survival at 6 months. No severe adverse events were reported[18].

A single-centre double-blinded controlled trial was performed to assess FMT efficacy in UC patients with chronic pouchitis, a condition defined by chronic inflammation of the ileal pouch-anal anastomosis. The intervention consisted of 2 FMT doses delivered by endoscopy at week 0 and by enema at week 4 compared to autologous transplants (placebo). Twenty-six patients were included. Nine patients treated by FMT and 8 patients in the placebo group relapsed during the 52-week follow-up. No difference was observed between groups for the relapse-free survival (p-value = 0.183, log-rank; hazard ratio, 1.90 [95% confidence interval,

0.73-4.98; *p*-value = 0.190]). No major adverse events were reported. However, a lack of power because of the small number of patients included limited interpretation of these results[19].

OTHER STUDIES ON FMT IN IBD

To assess secondary IBD-related outcomes after a single FMT dose for recurrent *C. difficile* infection (CDI), Allegretti et al[29] presented a new analysis from an open-label, prospective, multicenter cohort study. Fifteen patients with CD and 35 patients with UC were included. Seventy-three percent of CD patients (11/15) reported symptom improvement based on the Harvey-Bradshaw index. In UC, 62% (22/34) had an improvement based on the Mayo score, and only 1 patient reported a *de-novo* flare. In parallel, alpha diversity of fecal microbiota increased after FMT.

Perception and acceptability of FMT for patients with IBD has been also explored. In a small series of 8 UC pediatric patients, FMT was perceived as a natural treatment with a good acceptability[33]. In line with the "natural perception" reported, the use of self-FMT in IBD outside the scope of clinical trials or medical guidance is now a reality. An internet survey in the USA reported that among 3274 IBD patients, 51 (1.6%) had received FMT in the past; twenty-two for recurrent CDI and 29 for another indication[23]. In this latter category, only 20.6% of patients had involved a medical professional, exposing themselves to potential harmful side-effects. Patient-reported efficacy was quite low compared to the literature in CDI (63.6%; 14/22) and even lower when performed for other indications (10.3%; 3/29). Regarding, predictors of FMT efficacy in IBD, an increase in *F. prausnitzii* and *Akkermansia muciniphila* in the microbiota of UC patients after FMT was associated with an improved clinical response[18,30,34]. A high Candida abundance in the microbiota of UC patient *pre*-FMT and a decreased Candida abundance *post*-FMT were also associated with clinical response[35]. Re-analysis of a possible donor-effect using original data from 10 controlled trials did not demonstrate a clear donor effect despite some data not being available in all existing trials with more studies needed to confirm authors' conclusions[36]. Based on the results of a RCT in CD, Kong et al[37] reported long-term effect of FMT on recipient microbiota with engraftment of donor's species at the strain level. Engraftment of Actinobacteria, and engraftment or loss of Proteobacteria, were related to better clinical outcome, while transmission of Bacteroidetes was deleterious.

Combining different *in vitro* approaches, Hiippala and colleagues isolated from a fecal donor 7 strains of the *Bacteroides* genus (*P. distasonis*, *B. caccae*, *B. intestinalis*, *B. uniformis*, *B. fragilis*, *B. vulgatus* and *B. ovatus)* with anti-inflammatory properties as defined by their ability to attenuate *E. coli* lipopolysaccharide (LPS)-induced interleukin 8 (IL-8) release from HT-29 cells[38]. In another work, Britton et al[39] revealed novel crosstalk mechanisms between the Treg compartment and the gut microbiota following FMT. FMT of healthy-donor derived microbiota in mice colonized with human IBD microbiota induced expansion of RORgT + regulatory T cells, an increase in fecal microbiota density and a decrease in Th17-inducer bacteria which conferred protection from colitis. In a rat model of dextran sulphate sodium (DSS)-induced colitis, one FMT was also associated with a less severe phenotype and a shift in gut microbiota composition towards the FMT donor[40]. Along the same lines, previous exposure of the donor to vancomycin or streptomycin affected the anti-inflammatory properties of FMT after DSS while pretreatment by metronidazole did not. Interestingly, donor exposure to metronidazole favoured *Lactobacillus* enrichment after FMT and polarization of innate Natural Killer cells to the production of the anti-inflammatory interleukin-10[41].

Studies testing probiotics use in IBD context were published, of which two were clinical trials. As ulcerative colitis (UC) patients have a reduced level of Firmicutes and of their associated metabolites, the safety and efficacy of an oral formulation of Firmicutes spores were evaluated in a phase 1b trial[42]. The 58 enrolled patients received a preconditioning with oral vancomycin or placebo followed by 8 weeks of the oral microbiome drug or placebo. Engraftment of the drug and changes in microbiome composition and associated metabolites were measured by analyses of stool specimens collected at different times. The oral microbiome drug after vancomycin preconditioning was significantly more effective than placebo for induction of remission in patients with active mild to moderate UC. A phase 2b trial needs to be conducted to confirm these results.

A double-blind, placebo-controlled, pilot study was performed to investigate the effect of a colonic-delivery formulation of butyrate on the fecal microbiota of IBD patients. In addition to conventional therapy, 49 IBD patients received microencapsulated-sodium- butyrate or placebo for 2 months[43]. After treatment, IBD patients who received the sodium-butyrate supplementation showed an increase in the growth of short-chain fatty acids (SCFAs) producing bacteria, some with potential anti-inflammatory action. However, further investigations are needed to precise the clinical impact of such intervention.

MICROBIOTA CHANGES WITH DRUG THERAPIES

The microbiota alterations during IBD treatment were the focus of nine studies and there has been significant interest in harnessing changes in microbial profiles as biomarkers for disease diagnosis, disease activity, treatment response, and outcome prediction. Six of these studies focused on anti TNF alpha medications (mostly infliximab) while other studies focused on azathioprine, glucocorticoids and autologous hematopoietic stem cell transplantation.

A small single centre Korean study[44], comprising 40 IBD subjects in clinical remission and 10 healthy controls, assessed alterations in intestinal microbiota using 16S rRNA gene-based microbiome profiling during an 8-week infliximab maintenance treatment. Fecal samples were collected at week 1 and week 7 and microbial analysis according to trough levels of infliximab (TLI) and mucosal healing status (MH) was conducted. No significant changes in microbial composition, species richness, or diversity indices between the two timepoints were observed. However, in patients with TLI ≥ 5 µg/mL, there was an increase in species richness and distinct species taxa abundances (*Bacteroides uniformis, Faecalibacterium prausnitzii* group*, Intestinibacter bartlettii, Bacteroides thetaiotaomicron, Corprococcus comes group, LT635539_s group, and Citrobacter murliniae*) compared to patients with TLI < 5 µg/mL. The MH group was observed to have significantly higher abundance of genera F*aecalibacterium, Blautia,* and *Bacteroides*, and lower abundance of *Prevotella* compared to the non-MH group. Notably, the *Bacteroides* to *Prevotella* ratio of the MH group was significantly higher than that of the non-MH group and was closer to ratios from healthy controls. In particular, *F. prausnitzii* was identified as a potential biomarker for therapeutic TLI and MH, however, its utility as a response indicator was not explored. A second study by Zhuang et al[45] further evaluated the predictive value of using microbiota alterations to predict treatment response to infliximab. Using 16S sequencing, the fecal microbiota of 49 patients with active CD were analysed at baseline, week 6 and week 30. They found that patients on infliximab therapy displayed an increased diversity and richness, especially with an increased abundance in SCFA producing bacteria including *Bacteroidetes* and *Firmicutes*, and a loss of pathogenic bacteria such as *Proteobacteria*. More importantly, higher abundances of *Lachnospiraceae* and *Blautia* were associated with infliximab efficacy and their combined increased early in week 6 showed 83.4% and 84.2% accuracy in predicting clinical response at weeks 14 and 30 respectively, and a predictive value of 89.1% in predicting endoscopic response at week 30. Although the results are promising, the study was small and requires validation in additional datasets. Ventin-Holmberg and colleagues looked at both bacterial and fungal changes during infliximab therapy and assessed their associations with treatment outcomes[46]. Analysis of fecal samples of 25 CD and 47 UC patients were done at baseline, 2, 6, 12 weeks and 1 year post initiation of therapy. In concordance with current literature, both bacterial and fungal profiles were distinctly different between response groups at baseline. Non-responders had decreased abundance of SCFA producers including *Clostridia* and *Candida*, compared to responders. The findings, together with results from current literature, demonstrates the promising potential of using gut microbiota as biomarkers to predict treatment responses.

Ding et al[47] assessed metabolic biomarkers of anti-TNF response in a CD cohort – the largest longitudinal cohort study of CD patients to date to investigate metabonomic and metataxonomic profiling. The study, comprising 76 anti-TNF naive CD patients and 13 healthy controls identified metabolic profiles predictive of primary non-response in CD patients on anti-TNF therapy with alterations in bile acids, amino acid and lipid metabolites. Histidine and cysteine were identified as serum and urine biomarkers of response. Lipid profiling of serum and feces

found phosphocholine, ceramides, sphingomyelins, and triglycerides, and bile acid profiling identified primary bile acids to be associated with non-response to anti-TNF therapy, with higher levels of phase 2 conjugates in non-responders. In agreement with other studies, the authors demonstrate that anti-TNF therapy response is individualised. Mavragani et al[48] focused on a different target and investigated whether type I and II interferon signatures could predict response to anti-TNF therapies by analysing peripheral blood samples for type I and type II IFN genes (IFNGs) from 30 IBD patients and 10 healthy controls at baseline and after treatment. At baseline, type I IFN score was significantly higher in IBD patients (p-value= 0.04 *vs*. controls). Responders to subsequent anti-TNF treatment had significantly lower baseline scores for both type I and II IFN signatures. During treatment with anti-TNF, the expression of type I and II IFNGs was significantly elevated in responders and decreased in nonresponders. Between responders and nonresponders to anti-TNF therapy, *Micrococcus*, *Dialister*, *Glutamicibacter*, *Coprococcus 3*, *Geobacillus*, and *Negativibacillus* appear to influence IFN I levels, whereas *Barnesiella*, *Bifidobacterium*, *Ruminococcus gnavus*, *Ruminococcaceae*, and *Clostridium senso stricto* are postulated to influence IFN II levels in responders. For the nonresponders group, IFN I was best predicted by *Gardnerella*, *Exiguobacterium*, *Lachnospira*, *Parabacteroides*, and *Subdoligranulum* and IFN II by *Kocuria, Ruminoclostridium 9, Haemophilus, Coprococcus 1*, and *Bifidobacterium.* The role of using type I and II IFNs signatures to predict therapy responses is promising but currently lacks independent validation studies.

A few studies evaluated the association between gut microbiota alterations and/or metabolic profiles and therapy responses with azathioprine, glucocorticoid or autologous hematopoietic stem cell transplantation. A comprehensive study involving IBD patients on azathioprine and anti-TNF therapy was conducted by Effenberger et al[49]. Longitudinal changes in taxa composition at phylum level revealed a significant decrease in Proteobacteria and an associated increase in Bacteroidetes during treatment, with SCFA production found to be associated with long-term disease remission. Importantly, the authors observed an increased Lactobacilli abundance was associated with persistent disease and increased Bacteroidetes abundance was associated with remission in CD. With the use of *in-silico* metabolic prediction analysis of microbial metabolite exchange, the authors found that patients in remission had a 1.7 times higher butyrate production capacity than those not in remission. In a small Chinese study involving 17 UC patients, differences in intestinal microbiota composition and its associated metabolic pathways were analysed based on patients' responses to glucocorticoids: glucocorticoid sensitive, glucocorticoid resistant and glucocorticoid dependent. Zhu et al[50] found that gut microbial profiles in UC patients with different response types were significantly different, suggesting that metabolic pathways in these patients will vary as well. Functional prediction and KEGG enrichment analysis of differential bacterial communities revealed that "PANTO-PWY: phosphopantothenate biosynthesis I", "COA-PWY-1: coenzyme A biosynthesis II (mammalian)" and "PWY-4242: pantothenate and coenzyme A biosynthesis III" metabolic pathways were differently enriched among the groups. Although both studies did not thoroughly explore the efficacy of these distinct microbial changes on predicting treatment response, insights from both studies will lay the foundation for future research.

Published in Nature Communications, Metwaly et al[51] performed a gut microbiome and metabolite analysis of a longitudinal cohort of CD patients undergoing autologous hematopoietic stem cell transplantation. Comparisons between responders who maintained remission, responders who relapsed and non-responders revealed shared functional signatures that correlated with disease activity. Subsequent predictive modelling of disease outcomes was conducted using an integrative multi-omics approach in gnotobiotic mice which enabled the identification of functional biomarkers associated with therapeutic failure including sulphur dissimilation and bile acid detoxification or treatment success.

Conflict of interest

E.B., G.H., C.M. declare no conflict of interest. H.S. received consultancy, or lecture fees, from Carenity, Abbvie, Astellas, Danone, Ferring, Mayoly Spindler, MSD, Novartis, Roche, Tillots, Enterome, Maat, BiomX, Biose, Novartis, and Takeda and is also a co-founder of Exeliom Bioscience. N.B. received lecture fees from Tillots.

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