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Review article

Fecal microbiota transplantation for the treatment of chronic inflammatory skin diseases

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ABSTRACT

The regulation of immune functions and the maintenance of homeostasis in the internal environment are both integral to human gut microbiota (GM). If GM is disturbed, it can result in a range of autoimmune diseases, including chronic inflammatory skin conditions. Chronic inflammatory skin diseases driven by T or B-cell-mediated immune reactions are complex, including the most prevalent diseases and some rare diseases. Expanding knowledge of GM dysbiosis in chronic inflammatory skin diseases has emerged. The GM has some causal roles in the pathogenesis of these skin conditions. Targeting microbiota treatment, particularly fecal microbiota transplantation (FMT), is considered to be a promising strategy. FMT was commonly used in intestinal diseases by reshaping and balancing GM, serving as a reasonable administration in these skin inflammatory diseases. This paper summarizes the existing knowledge of GM dysbiosis in chronic inflammatory skin diseases and the research data on FMT treatment for such conditions.

1. Introduction

A massive medical load has been caused by the prevalence of persistent inflammatory skin diseases, with atopic dermatitis (AD) and psoriasis being the most prevalent [1]. In addition, autoimmunity can be a contributing factor to conditions such as alopecia areata (AA), pemphigus and pemphigoid diseases, vitiligo, and chronic spontaneous urticaria, all of which are caused by T cells or B cells dysregulation. There are a few rare causes of chronic skin inflammation, including autoinflammatory diseases or rheumatic diseases, such as cutaneous lupus erythematosus (CLE), Sjögren's syndrome (SjS), and Behçet's disease (BD) [2].

Knowledge of gut microbiota (GM) dysbiosis in chronic inflammatory skin diseases has increased [3]. The interaction between

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intestinal epithelial cells and activation of immune cells has been suggested as a potential cause of various immune disorders attributed to GM dysbiosis [4–6]. Given the correlation of psoriasis phenotypes with gut microbes, there seems to be a powerful positive association between an increased abundance of *Phascolarctobacterium* species and proinflammatory cytokines, which could be pertinent to T-cell activation [7]. By regulating the proportion of T-cells and altering the composition of GM, *Lactobacillus paracasei KBL382* isolated from healthy people has been shown to alleviate AD-like symptoms and symptoms of obesity [8]. Consequently, it is valuable to explore the relationship between gut microbiota (GM) dysbiosis and chronic inflammatory skin diseases, as well as consider fecal microbiota transplantation (FMT) as a proposed treatment for targeting these skin diseases. In our narrative review, the literature research was performed by searching the PubMed database, and adopting the search terms (fecal microbiota transplantation) OR (gut microbiota) AND (chronic inflammatory skin diseases).

2. FMT under clinical development for chronic inflammatory skin diseases

In humans, the intestinal microbiota is necessity for stimulating, educating and sustaining the immune system's equilibrium [9]. It is estimated that there are more than 1000 species-level phylotypes in human intestinal environments [10], of which Bacteroidetes and Firmicutes account for 90 percent [11]. As researchers delve into the links between GM composition and susceptibility to disease, as well as how commensal microbiota and their metabolites affect human health, they are being spurred on to investigate targeted microbiota-based therapies [12].

The first proposal for FMT in pseudomembranous colitis was made in 1958 [13]. The well-documented and effective GM-management strategy involves injecting healthy donor feces into the intestinal tract of the patient. Aiming to improve probiotic status, remodel a healthy GM, and reinstate its beneficial functions. For more than 40 years, FMT has been reported widely as a therapy for recurrent *Clostridioides difficile* infection [14], which is typically an antibiotic-induced dysbiosis.

2.1. Atopic dermatitis

In recent years, a correlation has been found between changes in gut microbes and the occurrence of AD [15]. Specific characteristics of the GM in 3-month-old breast-fed infants showed greater abundance of *Clostridium sensu stricto*, which is thought to be related to AD [16]. This observation was the confirmation of similar alpha-diversity, partial differences in beta-diversity, and positive correlations in the abundance of *Gemella* species in allergic infants [17]. A cross-sectional investigation of 81 Brazilian children aged 5 to 11 revealed a correlation between AD and the greater numbers of *Clostridium difficile*, *Bifidobacterium* species, as well as lesser amounts of *Lactobacillus* species within their intestinal microbiota [18]. Patients with AD exhibited a reduction in GM diversity in comparison with healthy individuals, and the richness of conducive symbiotic microbes, such as *Lactobacillus* species and *Bifidobacterium* species, was notably diminished; however, the proportions of *C. difficile*, *Escherichia coli*, and *Staphylococcus aureus* were increased significantly [19]. One study showed that individuals with AD had a relative abundance of bacteria of the order Bacteroidales and Bacteroidia, phylum Bacteroidetes, and genera *Romboutsia* and *Sutterella* [20]. Similar to the skin, *S. aureus* was found to be abundant in the GM of patients suffering from AD [21]. According to a birth cohort study conducted in Sweden, *S. aureus* strains carrying specific superantigens and adhesins colonized the gut during early childhood would cause AD in those children later [22]. SCFAs are microbial metabolites in the human gut with anti-inflammatory effects. A significantly reduced risk of AD has been linked to a high concentration of SCFAs and copious amounts of butyrate-producing bacteria (BPB), such as *Coprococcus eutactus*, in fecal material [23–25]. Early life colonization and alteration of the GM occurs before the presentation of clinical manifestations, indicating that GM dysbiosis may be a contributing factor to AD [26,27].

Kim et al. initially put the emphasis on using FMT in AD therapy. It was shown that FMT had a potential therapeutic effect on AD-induced allergic symptoms in mice by restoring GM and immunologic balance (Th1 cells/Th2 cells) [28]. An oxazolone-induced AD mouse model was created. Mice were categorized into high-responding (HR) and low-responding (LR) donors determined by their dermatitis score, ear thickness, and concentrations of inflammatory cytokines. Feces materials from these AD mice were delivered into pregnant germ-free Swiss Webster dams and their progeny [27]. HR recipient mice exhibited higher clinical scores for dermatitis than LR recipient mice [29]. In a calcipotriol (MC903)-induced AD model, mice were treated with FMT from healthy mice for 7 days. The GM of the FMT group changed significantly during natural recovery, especially the increased Firmicutes: Bacteroidetes (F: B) ratio as well as BPB concentration. The mouse model of AD following FMT treatment, revealed a plethora of modifications in metabolic and immune pathways [30].

FMT was evaluated for the first time in humans at Tel Aviv Medical Center for adults with moderate to severe AD. The results showed a marked improvement from baseline in signs and symptoms of AD. Following each FMT, the average Scoring Atopic Dermatitis value decreased significantly at week 4. In the total of 9 participants, there were 7 and 6 patients achieved reduction of 50 % and 75 % at week 18 (after 8 weeks since the last FMT), respectively. However, two of the patients experienced quick relapse after treatment. The clinical results were hampered by the limited sample size, the lack of double-blinded design, and other factors that had to be taken into account [31]. For patients suffering from AD, FMT might be a safe and efficacious therapeutic intervention. Further explorations are required to confirm the immune response, gut metabolites, and AEs in clinical studies. There is a disruption in the gut barrier among AD patients, which makes them more vulnerable to the risks of FMT [32].The development of alternative GM-targeted therapies by combining appropriate microorganisms or microbial metabolites may therefore be a rational approach for treating AD in the future.

2.2. Psoriasis

GM in patients with psoriasis exhibits a diminished bacterial diversity and a variance in beta-diversity [33]. A greater decrease in biodiversity is observed in patients with moderate-to-severe psoriasis than in those with mild psoriasis [34]. GM composition is also distinct in patients, as *Firmicutes*, *Actinobacteria*, *Verrucomicrobia*, *Faecalibacterium*, *Bacteroides*, *Bifidobacterium, Megamonas* and *Roseburia* have higher abundances; whereas the phyla *Bacteroidetes*, *Euryarchaeota*, *Proteobacteria* and genera *Prevotella*, *Alistipes*, and *Eubacterium* are less abundant [35,36].

Psoriasis has been associated with the GM in many studies [7,37–40]. This is evidenced by the augmented F:B ratio, a sign of a weakened gut epithelial barrier of patients [37], which induces microbial movement from the gut to the bloodstream. Additionally, it has also been found that "leaky" bacterial DNA in the bloodstream of psoriatic patients, which is considered to derive from the intestinal lumen, contributes to the development of psoriatic plaques [38]. Psoriasis may be induced by GM variations, resulting in dysregulation of inflammation-related biomarkers and an abnormal immune response. In particular, IL-2 receptors interact positively with *Phascolarctobacterium* species and negatively with *Dialister* species. Therefore, the relative abundance of those strains could provide the clue of the severity of psoriasis in psoriatic patients [7]. The GM, in an experimental mouse model of psoriasis caused by TLR7 agonist imiquimod, augmented the Th17 response [39]. Broad-spectrum oral antibiotics administration could reduce the skin inflammation of mouse model by decreasing the Th17 immune response [40].

An experiment was conducted on mice that presented with psoriatic dermatitis and colitis. The imiquimod and dextran sulfate sodium (DSS) was administered to the rodents. Those given imiquimod experienced an abrupt onset of DSS-induced colitis, with a reduction in immunoglobulin (Ig)D^+ and IgM^+ B cells as well as a rise in noncytokine-producing macrophages in the gut. The GM composition of mice treated with imiquimod was significantly altered, with a decrease in the population of Lactobacillus species, which are implicated in causing severe DSS-induced colitis [41]. Further experiments demonstrated that IQI/Jic mice suffering from DSS-induced colitis experienced exacerbation when feces from imiquimod-treated mice were transplanted into them [41]. Conversely, the fecal microbiota of healthy individuals, when transplanted into imiquimod-induced mice, caused a remarkable reduction in skin inflammation, suggesting that the Tregs/Th17 cell imbalance observed in psoriasis could be remedied through this method [42]. Another study verified bacteria of the family *Ruminococcaceae* and genera *Coprococcus_1* and *Blautia* were less plentiful in mice with psoriasis that received fecal microbiota from patients with psoriasis and their psoriasiform dermatitis took longer time to recover [43].

In a case, a 36-year-old Chinese man had been suffered with severe plaque psoriasis for a decade, as well as IBD for fifteen years, was the first to be described in a clinical case report regarding FMT application. During the five-week interval between administrations, FMT was administered twice through upper endoscopy and colonoscopy. At the endpoint, the serum concentration of TNF-α as well as Psoriasis Area and Severity Index were reduced in comparison to their baseline state, while histology and intestinal symptoms were both improved [44]. In 2015, the first proof-of-concept, a parallel-group, double-blind placebo-controlled, a single-center superiority trial was carried. The results showed that FMT is safe but not more effective than sham for active peripheral psoriatic arthritis. Thirty-one participants were enrolled. Serious AEs were not seen during the whole treatment peroid. The FMT group exhibited a significantly higher prevalence of treatment failure (defined as needing more than one intra-articular glucocorticoid injection, non-methotrexate conventional synthetic and/or biologic DMARD) than the sham group (transplant saline in the duodenum using an oral-duodenal tube), which was largely linked to AEs in gastrointestinal tract issues such as abdominal unease, flatulence, nausea, and vomiting [45]. Consequently, FMT is considered to be a safe administration for psoriasis, but the efficiency needs to be verified by larger sample size research.

2.3. Alopecia areata

A comparison of stool samples in AA and control groups did not reveal significantly different alpha- or beta-diversities in the GM. However, those with AA displayed an augmented abundance of bacteria of the families Erysipelotrichaceae, Lachnospiraceae, as well as *Holdemania filiformis*, *Parabacteroides johnsonii*, *Clostridiales vadin BB60* group, *Bacteroides eggerthii*, and *Parabacteroides distasonis* [46]. In contrast to healthy controls, a survey of Chinese people demonstrated that the GM in the AA group showed markedly more abundance in the family Erysipelotrichaceae, the genera *Blautia*, *Anaerostipes*, *Dorea*, *Collinsella*, *Megasphaera*, and *Achromobacter* than those in healthy controls, while the family Fusobacteriales showed a lower abundance [47]. It is possible that the GM contributes to AA development either by preventing fiber intake or by lowering SCFA-producing bacteria. This could result in a decrease in bacterial SCFA synthesis, thus leading to a decreased Treg-associated peripheral tolerance [48,49]. Genetically susceptible individuals may be at risk for immune system stress caused by gut dysbiosis [50]. A pilot study found shifts in the GM in pediatric patients with AA and identified that *Ruminococcus bicirculans* abundance was reduced in children (4–17 years) with AA in comparison with the siblings without AA [51].

Preventive treatment of AA is not available. Hence, targeting the GM with FMT has become a candidate treatment for AA [52]. After FMT, hair regrowth occurred in two patients with recurrent *C. difficile* infection accompanied by alopecia universalis [53]. In a 86-year-old patient with patchy AA and noninfectious diarrhea, hair regrew in the affected areas, and gray hairs gradually turned black after FMT [54]. Therefore, FMT is considered a potential therapy for patients with AA. To authenticate the part FMT plays in AA, further extensive and specialized research is necessary.

2.4. System lupus erythematosus

There was a significantly low F:B ratio observed in individuals with SLE in the first report on SLE-associated intestinal dysbiosis

[55]. Except for two research groups that showed there was no alteration [56] or an ~1-fold increase in the F:B ratio in patients with SLE [57], many studies subsequently revealed the same finding [58,59]. The genera *Streptococcus*, *Campylobacter*, and *Veillonella* had a positive correlation with SLE activity in the turbulent microbiota, whereas *Bifidobacterium* species had a negative association [58]. In Spain, bacteria of the genera *Rhodococcus*, *Eggerthella*, *Klebsiella*, *Prevotella*, *Eubacterium*, *Flavonifractora*, and *Incertae sedis* were demonstrated to be clearly thrived among patients with SLE, whereas the *Dialister* species and *Pseudobutyrivibrio* species had a dramatic decline [60]. In southern China, the GM of individuals with SLE was observed to have a notable rise in the abundance of the phylum Actinobacteria and *Ruminococcus gnavus* [61]. Interestingly, a remarkable distinction in GM composition between male and female littermates at adult ages was observed in a mouse model with SLEs [62]. There was no change in the alpha-diversity of the GM among children with SLE, but a partial decrease in the beta-diversity [63]. There were lower alpha-diversities and altered beta-diversities in adult SLE patients and mouse models [56,60], which were directly paralleled with the SLE Disease Activity Index (SLEDAI) score [64]. Due to the translocation of *Enterococcus gallinarum* to systemic organs, autoimmune-prone patients and mice showed autoimmune reaction and lupus typical serological features [65].

Many experimental studies were conducted to investigate the effectiveness of FMT in treating SLE in mice [66–69]. Consumption of acidic water drinking could correct the GM composition in mice with SLE, and transfer of this integrated GM *via* FMT could control SLE progression in mouse models [68]. Next-generation sequencing revealed that the fecal microbiota of germ-free mice that received transplants from donors with SLE had the exact same microbiota as their donors. The fecal microbiota of mice with SLE led to a significant rise in antibodies to double-stranded (ds)DNA. This, in turn, caused a noteworthy disturbance in the spread of immune cells, increased expression of SLE-susceptible genes, and accelerated the development of autoimmunity [70]. In MRL/MPJ-Faslpr (MRL-lpr) mice, a particular type of lupus-prone mouse model, the beneficial outcome was demonstrated through early and short-term FMT interventions. The richness of *Prevotella* species in the intestines of MRL/lpr mice with pristane-induced SLE was significantly increased, which was positively correlated with cyanogen amino-acid metabolism and many different metabolites [71]. FMT treatment following 1 week of short-term antibiotic exposure suppressed SLE progression. However, the therapeutic efficacy of prednisone was inhibited in mice aged 9–13 weeks when antibiotics or FMT were used for short-term before onset of SLE [66]. That result suggested that undertaking FMT treatment before SLE onset could decrease the severity and suppress the progression of SLE, but it should be considered cautiously for patients who are treated routinely with glucocorticoids.

Recently, the MRL/lpr mice provide new evidence that FMT, which is derived from prednisone-treated therapy mice to blank one, can reduce lupus activity. The efficiency is similar to prednisone, but no parallel adverse reactions. The finding may be due to the decreased abundances of *Ruminococcus* species and *Alistipes* species, whereas the abundance of *Lactobacillus* species remained unchanged [67]. Those data suggest that a combination of FMT and glucocorticoid therapy might be efficacious, but further study is needed. Germ free (GF) mice that accepted FMT from the one who suffered from SLE displayed a range of SLE-like characteristics, such as the augmented presence of autoimmune antibodies, abnormal release of cytokines, altered immune responses, and higher expression of SLE-related genes [69]. Environmental factors as well as the GM work in concert in the development of the sex-based bias seen in SLE. In female MRL/lpr mice, the GM is associated with higher SLE indices than in male mice. This has been linked to the presence of more bacteria of the genera *Rikenella*, *Romboutsia*, *Turicibacter,* and *Escherichia-Shigella* [72]. Recent findings have demonstrated upregulation of methylation at multiple sites after FMT treatment of SLE, thereby revealing a possible mechanism by which FMT therapy may restore abnormal hypomethylation [73]. Overall, those evidences describe an “ideal” role of FMT in recovering from the progress of SLE.

Clinical trials of FMT as a treatment of SLE (e.g., ChiCTR2000036352) have been carried out since 2020 [74]. During a 12-week pilot study, 20 patients with active SLE received FMT as an additional treatment. For 3 consecutive weeks, these patients received encapsulated fecal microbiota by oral administration once a week. At the final evaluation period, there was a considerable reduction in SLEDAI-2K ratings and serum anti dsDNA antibody concentrations, and no noticeable serious adverse events were seen compared to the initial assessment. There was a significant rise in the population of bacteria that produce SCFAs, a significant decrease in bacteria that produce substances related to inflammation, a large amount of SCFAs in the gut led to a decrease in cytokine levels associated with inflammation, and a change in the ratio of $CD4^+$ memory cells to naive cells in peripheral blood [74]. Subsequent single-cell analysis of peripheral blood revealed a decrease in T cells and an increase in natural killer cells. After FMT treatment, subcluster analysis revealed an overexpression of IL7R and CD28 in the total number of $CD4^+$ T cells, as well as granzyme H (GZMH) and natural killer cell granule protein 7(NKG7) in $CD8^+$ T cells. Additionally, interferon-associated genes expression was found to be decreased in $CD4^+$, $CD8^+$, double positive (DP), natural killer, and B cells [75]. There was a greater abundance of interferon-related pathways in patients who were unresponsive to FMT. The efficacy of FMT was negatively associated with interferon-related genes expressed in lymphocytes and myeloid cells. This preliminary clinical trial of FMT in patients with active SLE offers encouraging proof that it could be a novel, safe, and efficacious treatment for SLE.

2.5. Sjögren’s syndrome

One hypothesis presumed a communication route called the “gut dysbiosis–ocular surface–lacrimal gland axis” in the pathogenesis of SjS [76]. A deeper analysis of the GM of patients with SjS through metagenomic sequencing revealed a remarkable reduction in the number of operational taxonomic units and Shannon alpha-diversity in comparison with those in healthy controls [77]. In comparison to controls, those with SjS had a greater relative abundance of bacterial genera *Pseudobutyrivibrio*, *Escherichia/Shigella*, *Blautia*, and *Streptococcus*, whereas the bacterial genera of *Bacteroides*, *Parabacteroides*, *Faecalibacterium*, and *Prevotella* were less plentiful abundant than that in controls [78]. In patients with SjS and dry eyes, Firmicutes are the most common phyla in the gut, followed by Bacteroidetes, Proteobacteria, and Actinobacteria [79]. In a study from China, the bacterial genera *Bifidobacterium*, *Bacteroides*,

Escherichia-Shigella, *Faecalibacterium*, and *Prevotella* were notably prevalent in females with SjS [80]. Based on GM profiles of patients with primary SjS, diversity and richness were lower, and *Bacteroidetes* dominated at the phylum level, as one study described. The prevalence of opportunistic pathogens with proinflammatory activity was higher in patients with primary SjS and fewer beneficial bacteria or commensal bacteria produced butyrate. The peripheral area was affected by an increase in proinflammatory cytokines and a decrease in forkhead box P3 (FOXP3) mRNA expression due to this scenario [81]. Those with serious GM dysbiosis exhibited more intense disease activity, as assessed by the European Alliance of Associations for Rheumatology Sjögren's Syndrome Disease Activity Index and Clinical European Alliance of Associations for Rheumatology Sjögren's Syndrome Disease Activity Index scores. Additionally, they had a reduced complement component 4 and a high fecal calprotectin concentration [82].

Mice with SjS were treated with FMT in an experimental model of dry eye. A study delving into the part of commensal bacteria uncovered that germ-free mouse had transferable, spontaneous SjS-like lacrimal keratoconjunctivitis with a disruption of corneal barrier, fewer goblet cells and an abundance of total inflammatory cells and $CD4^+$ T cells. Difference was not seen in stool microbiota composition between recipients and donors after FMT, while FMT inhibited proliferation of autoreactive $CD4^+$ T cells in the lacrimal gland of vessels, reversed corneal epithelial barrier integrity, and restored goblet cell density [83]. Similarly, CD25-knockout mice spontaneously developed SjS-like inflammation. The dry-eye phenotype in germ-free CD25-knockout mice was reversed by fecal transplantation, and the formation of pathogenic $CD4^+$ interferon-γ^+ cells were reduced, suggesting that FMT treatment might reduce the onset and intensity of dacryoadenitis in SjS. Comparable corneal-barrier dysfunction, reduced density of goblet cells, and augmented lymphocytic infiltration were observed in these mice [84]. FMT from patients with SjS into germ free C57BL/6J female mice caused a disruption of corneal-barrier integrity and a decrease of $CD4^+$ $FOXP3^+$ cells in cervical lymph nodes. The progeny of SjS mice transplanted with FMT exhibited a comparable diminution in the amount of $CD4^+$ $FOXP3^+$ T_{regs} cells in their cervical lymph nodes. Above data implied that the GM traits of a parent could be passed down to offspring, potentially impacting the T_{reg} cells growth of the progeny [77].

The safety of FMT for patients with SjS and immune-mediated dry eye was initially evaluated in an open-label, non-randomized clinical trial [85]. The study enrolled 10 individuals with dry eye meeting the diagnostic criteria for SjS. Patients received two FMT procedures obtained from one single healthy donor by enema with a 1-week interval. The GM profiles of all patients were markedly dissimilar to those of the healthy donor, with a decrease in the genera *Faecalibacterium*, *Prevotella*, and *Ruminococcus*, and increased abundance of the genera *Alistipes*, *Streptococcus*, and *Blautia*. AEs were not observed, with certain bacterial profiles similar to those of the donor for up to 3 months. Five patients reported detectable improvements in the symptoms of dry eye [85]. That clinical trial suggested that FMT might be an effective treatment for dry eye, but future studies must involve a larger sample size and further modification of the regimen.

2.6. Behçet's disease

The pathogenesis of BD involves infiltration of hyperactive neutrophils and immune-mediated inflammation caused by *Streptococcus sanguinis* or microbiota changes [86]. A peculiar dysbiosis in the GM of 22 BD patients' fecal microbiota compared to that of 16 healthy cohabiting controls, with a notable decrease in *Roseburia* and *Subdoligranulum* and butyrate production. This could be linked to a reduction in T_{reg} responses and activation of immunopathologic responses of $T_{effector}$ cells [87]. Subsequent research showed that the abundance of the genera *Bifidobacterium* and *Eggerthella* had clearly increased, whereas that of *Megamonas* and *Prevotella* had decreased. In addition, the phylum Actinobacteria, which includes *Bifidobacterium* species and the Lactobacillaceae family, had a greater presence in those with BD. No noteworthy difference in alpha-diversity between samples was observed, the beta-diversity did vary slightly [88]. Shimizu and colleagues revealed that the relative abundance of *Eggerthella lenta*, *Acidaminococcus* species, *Lactobacillus mucosae*, *Bifidobacterium bifidum*, *Lactobacillus iners*, *Streptococcus* species, and *Lactobacillus salivarius* was enhanced significantly in BD patients, whereas the relative abundance of *Megamonas hypermegale*, *Butyrivibrio* species, *Streptococcus infantis*, and *Filifactor* species was diminished compared with that in healthy controls. Analysis of functional annotation showed that gene functions for the "pentose phosphate pathway" and "inosine monophosphate biosynthesis" were prevalent in patients with BD. Studies revealed that those afflicted with BD had the capacity to modify their nucleic acid and fatty acid synthesis through gut microbes [89]. Moreover, Ye and coworkers revealed that patients with BD had a elevated concentration of sulfate-reducing bacteria such as *Bilophila* species., as well as a few opportunistic pathogens like *Parabacteroides* species. and *Paraprevotella* species, and a lower concentration of BPB like *Clostridium* species, and methanogens such as *Methanoculleus* species and *Methanomethylophilus* species [90]. *Prevotella* is the major dysbiotic bacterial genus in neuro-BD [91]. Analysis of samples from two cohorts of BD sufferers in both the Netherlands and Italy was conducted to determine if alpha-diversity in the GM remained constant, while beta-diversity did not show any distinct clusters between the healthy controls and patients However, principal coordinate analysis showed that patients by country of origin had a significant ($p < 0.001$) separation. Patients exhibited a decrease in the fecal abundance of *Barnesiellaceae* and *Lachnospira* species, yet IgA-coating of *Bifidobacterium*, *Ruminococcus bromii*, and *Dorea* species was augmented, implying that anti-inflammatory species were retained and pathosymbionts neutralized in BD [92].

Due to the autoinflammatory features, one study in Turkiye compared the microbial composition among Behçet's Syndrome patients with uveitis, patients with familial Mediterranean fever and patients with CD. They found that Succinivibrionaceae was the signature family, whereas *Bacteroides* species were not observed in the BD group [93]. In a detailed analysis of the GM, alpha- and beta-diversity levels were not different between the BD group and controls, which was different from the previous study. The abundance of the bacterial genera *Actinomyces*, *Libanicoccus*, *Collinsella*, *Eggerthella*, *Enetrohabdus*, *Catenibacterium,* and *Enterobacter* was significantly higher in the BD group, whereas that of *Bacteroides*, *Cricetibacter*, *Alistipes*, *Lachnospira*, *Dielma*, *Akkermansia*, *Sutterella*, *Anaerofilum*, *Ruminococcease-UCG007*, *Acetanaerobacterium*, and *Copropaacter* was lower in patients with BD. Further comparison of

differences stratified by eye, mucocutaneous, and vascular involvement revealed the most significantly changed genera in each group, *Lachnospiraceae NK4A136* in the uveitis group; *Dialister*, *Intestinomonas*, and *Marvinbryantia* in the mucocutaneous group; and *Gemella* in the vascular group [94]. The diversity of the GM was found to be modified to suit the environment by employing a mouse model. In a specific pathogen-free facility, mice exhibited more bacterial phyla diversity and lower prevalence of BD compared to conventionally maintained mice. Those data suggested that a normal microbiota could affect BD induction, and that increasing the number of bacterial phyla was linked with inhibition of BD development [95]. Upon oral administration of *Eubacterium rectale*, the mouse model of BD (induced by herpes simplex virus type 1) demonstrated a decrease in $CD83^{+}$ cells and an inhibition of dendritic-cell activation and systemic inflammation [96].

Animals' experiments demonstrated that FMT with feces of patients with BD augmented the activity of experimental autoimmune uveitis significantly as well as increasing the level of inflammatory cytokines including IL-17 and interferon-γ [90]. As the community and functions of the GM in BD development become known, further clinical trials will become essential for BD treatment.

An overview of the published laboratory studies and clinical trials of FMT in chronic inflammatory skin diseases are given in Tables 1 and 2.

3. Conclusion and future perspective

The prevalence of chronic inflammatory skin disease is being linked to GM dysbiosis. As an essential method for reshaping and balancing GM, FMT serves as a reasonable administration in these diseases. A certain number of research evidence have indicated that FMT could alleviate persistent skin inflammation by restoring a healthy microbiota.

Although FMT has a very prospect for the treatment, it is still facing some challenges, such as infection risks and adverse reactions, and the compatibility of the microbiota of the donor and recipient remains a major concern. Nowadays, the widespread adoption of FMT as a standardized treatment is additionally hindered by regulatory factors and ethical concerns [97]. Engraftment of different donor strains has been ubiquitous across cohorts in studies. Administration route, antibiotic preconditioning and infectious diseases could also additionally interfere with the outcomes of FMT [98]. The risks of infectious transmission resulting from FMT are especially important [99]. Future standardized preparation of FMT with high quality and safety are urgently needed.

Due to the immune regulatory mechanisms of FMT, it has other potential values in the treatment for other skin conditions associated with GM imbalance, such as allergic contact dermatitis and melanoma. The efficacy of immunotherapy for melanoma is closely related to the gut microbiota [100]. FMT might assist the immunotherapy of melanoma by providing some favorable changes in immune and the tumor microenvironment, and it deserves further investigation. On the whole, it is imperative to address the existing knowledge gaps for future maximizing the potential of GM-targeted therapies and improving patient outcomes across a wider range of

Table 1
Animal studies using FMT against chronic inflammatory skin diseases.

Disorder	Source:	Outcome	reference
AD	Healthy donor mice	The GM was restored to the donor state after FMT, and SCFAs levels increased.	[28]
	Mice with oxazolone-induced dermatitis	The CDS and ET of HR recipients were significantly higher before treatment.	[29]
	Non-sensitized mice	FMT could suppress release of AD-related inflammatory cytokines.	[30]
Psoriasis	IMQ-treated mice	GF mice transplanted with IMQ-treated feces showed aggravated colitis.	[41]
	Healthy donors and patients with psoriasis	The symptom of psoriastic mice models administered with stools from psoriasis patient was worsened.	[42]
	Patients with moderate-to-severe psoriasis	After transplanting fecal microbiota from healthy human into a mice model of psoriasiform dermatitis, recovery was slowing.	[43]
SLE	Normal C57/BL6 mice	FMT alleviated the severity of SLE, and suppressed SLE progression.	[66]
	Prednisone-treated MRL/lpr mice	Prednisone-regulated GM alleviated SLE.	[67]
	Patients and healthy controls	SLE-related phenotypic changes were induced in GF mice after being transferred with feces from patients with SLE.	[69]
	C57/BL6 mice and SLE-prone mice to GF mice	Fecal microbiome from mice with SLE led to an elevation in the number of anti-dsDNA antibodies.	[70]
	MRL/lpr mice and MRL/Mpj mice	FMT from MRL/lpr mice exacerbated the pristane-induced SLE mice model.	[71]
SjS	Patients with SjS and healthy controls	Disruption of the corneal barrier in GF mice transplanted with fecus from SjS patients.	[77]
	Conventional C57BL/6J mice	The number of Th1 cells in the lacrimal gland of GF C57BL/6J mice with lacrimal keratoconjunctivitis was similar to SjS. FMT decreased the number of Th1 cells in the plasma and improved the corneal barrier.	[83]
	GF CD25KO mice	FMT improved recovery from a spontaneous dry eye phenotype and reduced the generation of pathogenic CD4+IFN-γ+ cells.	[84]
BD	32 patients with active BD and 74 healthy	B10RIII mice transplanted with fecus from BD patients, disease activity was exacerbated.	[90]

Abbreviations: AD: atopic dermatitis; SCFA: fecal short-chain fatty acid; GM: gut microbiota; Th: T helper cell; HR: high responding; CDS: Clinical Dermatitis Score; ET: ear thickness; GF: Germ free; IMQ: imiquimod; SLE: Systemic lupus erythematosus; SjS: Sjögren's syndrome; BD: Behçet's disease; dsDNA: double strains DNA; KO: knockout.

Table 2
Published clinical trials on use of FMT against chronic inflammatory skin diseases.

Disorder	Patient selection	Outcome details	Study type	reference
AD	9 patients with moderate (n = 4) and severe (n = 5) AD	The average SCORAD decreased obviously. The GM became similar to that of the donor after FMT.	Concept, single-blinded, placebo-controlled cross-over pilot study.	[31]
Psoriasis	a 36-year-old male, diagnosed with severe plaque psoriasis for 10 years and IBS for 15 years, was treated twice FMT with interim of 5-week	Evaluation items were significantly improved, and IBS was completely relieved after 5 weeks of second FMT treatment. No adverse reactions were found.	Case Report	[44]
Psoriasis	31 patients	No serious AEs or deaths were found in any group. Changes in HAQ-DI was decreased in the sham group than in the FMT group.	Double-blind, parallel-group, placebo-controlled, superiority trial.	[45]
AA	A 38-year-old AA patient presented with abdominal pain and bloody diarrhea and a 20-year-old man with ileocolic CD	New hair grew was shown on the head, face, and arms during the FMT follow up period.	Case Reports.	[53]
AA	A 86-year-old AA patient with noninfectious diarrhea, depressive disorder, and patchy	New hair was grown on the affected area of the scalp, and some gray hair gradually turned black after FMT.	Case Report.	[54]
SLE	20 SLE patients with SLEDAI $\geq$6	No serious AEs or deaths were found. Serum level of anti-dsDNA antibody fell significantly.	12-week, single-arm pilot clinical trial.	[74]
SjS	10 individuals with the symptoms and signs of dry eye received FMT	Five individuals had improved symptoms (gastrointestinal and dry eye) at the point of three months after FMT.	Open-label, nonrandomized clinical trial.	[85]

Abbreviations: AD:atopic dermatitis; SCORAD: Severity scoring of atopic dermatitis; DLQI: Dermatology Life Quality Index; IBS: Irritable Bowel Syndrome; AEs: adverse effects; HAQ-DI: Health Assessment Questionnaire Disability Index; CD: Crohn's Disease; AA: alopecia areata; SLE: system lupus erythematosus; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; dsDNA: double strains DNA; CTR: clinical trial registration; NCT: nonrandomized clinical trial; SjS: Sjögren's syndrome.

skin disorders.

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Data availability statement

Request on corresponding authors.

CRediT authorship contribution statement

Mingyang Wu: Resources, Investigation, Conceptualization, Writing – original draft, Writing – review & editing. **Xingyu Chen:** Writing – review & editing. **Qianjin Lu:** Writing – review & editing, Supervision, Conceptualization. **Xu Yao:** Conceptualization, Investigation, Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] M. Pasparakis, I. Haase, F.O. Nestle, Mechanisms regulating skin immunity and inflammation, Nat. Rev. Immunol. 14 (5) (2014) 289–301.
[2] H. Ujiie, et al., Unmet medical needs in chronic, non-communicable inflammatory skin diseases, Front. Med. 9 (2022) 875492.

[3] Š. Šuler Baglama, K. Trčko, Skin and gut microbiota dysbiosis in autoimmune and inflammatory skin diseases, Acta Dermatovenerol Alp Pannonica Adriat 31 (3) (2022) 105–109.
[4] I.I. Ivanov, K. Honda, Intestinal commensal microbes as immune modulators, Cell Host Microbe 12 (4) (2012) 496–508.
[5] K. Honda, D.R. Littman, The microbiota in adaptive immune homeostasis and disease, Nature 535 (7610) (2016) 75–84.
[6] E.M. Brown, D.J. Kenny, R.J. Xavier, Gut microbiota regulation of T cells during inflammation and autoimmunity, Annu. Rev. Immunol. 37 (2019) 599–624.
[7] X. Zhang, et al., Dysbiosis of gut microbiota and its correlation with dysregulation of cytokines in psoriasis patients, BMC Microbiol. 21 (1) (2021) 78.
[8] W.K. Kim, et al., Lactobacillus paracasei KBL382 administration attenuates atopic dermatitis by modulating immune response and gut microbiota, Gut Microb. 12 (1) (2020) 1–14.
[9] Y. Belkaid, O.J. Harrison, Homeostatic immunity and the microbiota, Immunity 46 (4) (2017) 562–576.
[10] C.A. Lozupone, et al., Diversity, stability and resilience of the human gut microbiota, Nature 489 (7415) (2012) 220–230.
[11] Structure, function and diversity of the healthy human microbiome, Nature 486 (7402) (2012) 207–214.
[12] J.S. Bajaj, S.C. Ng, B. Schnabl, Promises of microbiome-based therapies, J. Hepatol. 76 (6) (2022) 1379–1391.
[13] B. Eiseman, et al., Fecal enema as an adjunct in the treatment of pseudomembranous enterocolitis, Surgery 44 (5) (1958) 854–859.
[14] E. Gough, H. Shaikh, A.R. Manges, Systematic review of intestinal microbiota transplantation (fecal bacteriotherapy) for recurrent Clostridium difficile infection, Clin. Infect. Dis. 53 (10) (2011) 994–1002.
[15] S.Y. Lee, et al., Microbiome in the gut-skin Axis in atopic dermatitis, Allergy Asthma Immunol Res 10 (4) (2018) 354–362.
[16] T. Marrs, et al., Gut microbiota development during infancy: impact of introducing allergenic foods, J. Allergy Clin. Immunol. 147 (2) (2021) 613–621.e9.
[17] E. Łoś-Rycharska, et al., A combined analysis of gut and skin microbiota in infants with food allergy and atopic dermatitis: a pilot study, Nutrients 13 (5) (2021).
[18] L. Melli, et al., Gut microbiota of children with atopic dermatitis: controlled study in the metropolitan region of São Paulo, Brazil, Allergol. Immunopathol. 48 (2) (2020) 107–115.
[19] Z. Fang, et al., Gut microbiota, probiotics, and their interactions in prevention and treatment of atopic dermatitis: a review, Front. Immunol. 12 (2021) 720393.
[20] Y.J. Su, et al., Differences in gut microbiota between allergic rhinitis, atopic dermatitis, and skin urticaria: a pilot study, Medicine (Baltim.) 100 (9) (2021) e25091.
[21] B. Björkstén, et al., The intestinal microflora in allergic Estonian and Swedish 2-year-old children, Clin. Exp. Allergy 29 (3) (1999) 342–346.
[22] F.L. Nowrouzian, et al., Superantigens and adhesins of infant gut commensal Staphylococcus aureus strains and association with subsequent development of atopic eczema, Br. J. Dermatol. 176 (2) (2017) 439–445.
[23] H. Song, et al., Faecalibacterium prausnitzii subspecies-level dysbiosis in the human gut microbiome underlying atopic dermatitis, J. Allergy Clin. Immunol. 137 (3) (2016) 852–860.
[24] C. Roduit, et al., High levels of butyrate and propionate in early life are associated with protection against atopy, Allergy 74 (4) (2019) 799–809.
[25] L. Nylund, et al., Severity of atopic disease inversely correlates with intestinal microbiota diversity and butyrate-producing bacteria, Allergy 70 (2) (2015) 241–244.
[26] A.W. Arildsen, et al., Delayed gut colonization shapes future allergic responses in a murine model of atopic dermatitis, Front. Immunol. 12 (2021) 650621.
[27] L.F. Zachariassen, et al., Sensitivity to oxazolone induced dermatitis is transferable with gut microbiota in mice, Sci. Rep. 7 (2017) 44385.
[28] J.H. Kim, K. Kim, W. Kim, Gut microbiota restoration through fecal microbiota transplantation: a new atopic dermatitis therapy, Exp. Mol. Med. 53 (5) (2021) 907–916.
[29] K.P. Debes, et al., Betamethasone treatment for atopic dermatitis in gut microbiota transplanted mice, Comp. Med. 70 (1) (2020) 6–15.
[30] X. Jiang, et al., Fecal microbiota transplantation affects the recovery of AD-skin lesions and enhances gut microbiota homeostasis, Int Immunopharmacol 118 (2023) 110005.
[31] J. Mashiah, et al., Clinical efficacy of fecal microbial transplantation treatment in adults with moderate-to-severe atopic dermatitis, Immun Inflamm Dis 10 (3) (2022) e570.
[32] M.J. Alam, et al., Manipulating microbiota to treat atopic dermatitis: functions and therapies, Pathogens 11 (6) (2022).
[33] C. Hidalgo-Cantabrana, et al., Gut microbiota dysbiosis in a cohort of patients with psoriasis, Br. J. Dermatol. 181 (6) (2019) 1287–1295.
[34] I. Dei-Cas, et al., Metagenomic analysis of gut microbiota in non-treated plaque psoriasis patients stratified by disease severity: development of a new Psoriasis-Microbiome Index, Sci. Rep. 10 (1) (2020) 12754.
[35] S. Xiao, et al., Deciphering gut microbiota dysbiosis and corresponding genetic and metabolic dysregulation in psoriasis patients using metagenomics sequencing, Front. Cell. Infect. Microbiol. 11 (2021) 605825.
[36] M. Sikora, et al., Gut microbiome in psoriasis: an updated review, Pathogens 9 (6) (2020).
[37] Y.J. Chen, et al., Intestinal microbiota profiling and predicted metabolic dysregulation in psoriasis patients, Exp. Dermatol. 27 (12) (2018) 1336–1343.
[38] F.M. Codoñer, et al., Gut microbial composition in patients with psoriasis, Sci. Rep. 8 (1) (2018) 3812.
[39] Z. Zakostelska, et al., Intestinal microbiota promotes psoriasis-like skin inflammation by enhancing Th17 response, PLoS One 11 (7) (2016) e0159539.
[40] P. Zanvit, et al., Antibiotics in neonatal life increase murine susceptibility to experimental psoriasis, Nat. Commun. 6 (2015) 8424.
[41] H. Kiyohara, et al., Toll-like receptor 7 agonist-induced dermatitis causes severe dextran sulfate sodium colitis by altering the gut microbiome and immune cells, Cell Mol Gastroenterol Hepatol 7 (1) (2019) 135–156.
[42] H.L. Chen, et al., Gut and cutaneous microbiome featuring abundance of Lactobacillus reuteri protected against psoriasis-like inflammation in mice, J. Inflamm. Res. 14 (2021) 6175–6190.
[43] C. Sun, et al., Involvement of gut microbiota in the development of psoriasis vulgaris, Front. Nutr. 8 (2021) 761978.
[44] G. Yin, et al., [Fecal microbiota transplantation as a novel therapy for severe psoriasis], Zhonghua Nei Ke Za Zhi 58 (10) (2019) 782–785.
[45] M.S. Kragsnaes, et al., Safety and efficacy of faecal microbiota transplantation for active peripheral psoriatic arthritis: an exploratory randomised placebo-controlled trial, Ann. Rheum. Dis. 80 (9) (2021) 1158–1167.
[46] O.M. Moreno-Arrones, et al., Analysis of the gut microbiota in alopecia areata: identification of bacterial biomarkers, J. Eur. Acad. Dermatol. Venereol. 34 (2) (2020) 400–405.
[47] J. Lu, et al., Gut microbiota characterization in Chinese patients with alopecia areata, J. Dermatol. Sci. 102 (2) (2021) 109–115.
[48] M.B. Geuking, K.D. McCoy, A.J. Macpherson, Metabolites from intestinal microbes shape Treg, Cell Res. 23 (12) (2013) 1339–1340.
[49] P.M. Smith, et al., The microbial metabolites, short-chain fatty acids, regulate colonic Treg cell homeostasis, Science 341 (6145) (2013) 569–573.
[50] P. Sánchez-Pellicer, et al., How our microbiome influences the pathogenesis of alopecia areata, Genes 13 (10) (2022).
[51] S. Rangu, et al., Understanding the gut microbiota in pediatric patients with alopecia areata and their siblings: a pilot study, JID Innov 1 (4) (2021) 100051.
[52] Y. Kang, et al., The gut microbiome and Alopecia areata: implications for early diagnostic biomarkers and novel therapies, Front. Nutr. 9 (2022) 979876.
[53] D. Rebello, et al., Hair growth in two alopecia patients after fecal microbiota transplant, ACG Case Rep J 4 (2017) e107.
[54] W.R. Xie, et al., Hair regrowth following fecal microbiota transplantation in an elderly patient with alopecia areata: a case report and review of the literature, World J Clin Cases 7 (19) (2019) 3074–3081.
[55] A. Hevia, et al., Intestinal dysbiosis associated with systemic lupus erythematosus, mBio 5 (5) (2014) e01548, 14.
[56] X.M. Luo, et al., Gut microbiota in human systemic lupus erythematosus and a mouse model of lupus, Appl. Environ. Microbiol. 84 (4) (2018).
[57] J. He, et al., Microbiome and metabolome analyses reveal the disruption of lipid metabolism in systemic lupus erythematosus, Front. Immunol. 11 (2020) 1703.
[58] Y. Li, et al., Disordered intestinal microbes are associated with the activity of Systemic Lupus Erythematosus, Clin. Sci. (Lond.) 133 (7) (2019) 821–838.
[59] M. Guo, et al., Alteration in gut microbiota is associated with dysregulation of cytokines and glucocorticoid therapy in systemic lupus erythematosus, Gut Microb. 11 (6) (2020) 1758–1773.

[60] Z. He, et al., Alterations of the gut microbiome in Chinese patients with systemic lupus erythematosus, Gut Pathog. 8 (2016) 64.
[61] F. Wei, et al., Changes of intestinal flora in patients with systemic lupus erythematosus in northeast China, PLoS One 14 (3) (2019) e0213063.
[62] B.M. Johnson, et al., Gut microbiota differently contributes to intestinal immune phenotype and systemic autoimmune progression in female and male lupus-prone mice, J. Autoimmun. 108 (2020) 102420.
[63] M. Wen, et al., Correlation analysis between gut microbiota and metabolites in children with systemic lupus erythematosus, J Immunol Res 2021 (2021) 5579608.
[64] D. Azzouz, et al., Lupus nephritis is linked to disease-activity associated expansions and immunity to a gut commensal, Ann. Rheum. Dis. 78 (7) (2019) 947–956.
[65] S. Manfredo Vieira, et al., Translocation of a gut pathobiont drives autoimmunity in mice and humans, Science 359 (6380) (2018) 1156–1161.
[66] Y. Zhang, et al., Early and short-term interventions in the gut microbiota affects lupus severity, progression, and treatment in MRL/lpr mice, Front. Microbiol. 11 (2020) 628.
[67] M. Wang, et al., Gut microbiota mediated the therapeutic efficacies and the side effects of prednisone in the treatment of MRL/lpr mice, Arthritis Res. Ther. 23 (1) (2021) 240.
[68] B.M. Johnson, et al., Impact of dietary deviation on disease progression and gut microbiome composition in lupus-prone SNF1 mice, Clin. Exp. Immunol. 181 (2) (2015) 323–337.
[69] Y. Ma, et al., Lupus gut microbiota transplants cause autoimmunity and inflammation, Clin Immunol 233 (2021) 108892.
[70] Y. Ma, et al., Gut microbiota promote the inflammatory response in the pathogenesis of systemic lupus erythematosus, Mol Med 25 (1) (2019) 35.
[71] X. Yi, et al., Fecal microbiota from MRL/lpr mice exacerbates pristane-induced lupus, Arthritis Res. Ther. 25 (1) (2023) 42.
[72] C. Wang, et al., Gut microbiota mediated the effects of high relative humidity on lupus in female MRL/lpr mice, Adv Rheumatol 63 (1) (2023) 24.
[73] B. Zhang, et al., Effects of fecal microbiota transplant on DNA methylation in patients with systemic lupus erythematosus, J. Autoimmun. (2023) 103047.
[74] C. Huang, et al., Safety and efficacy of fecal microbiota transplantation for treatment of systemic lupus erythematosus: an EXPLORER trial, J. Autoimmun. 130 (2022) 102844.
[75] M. Zheng, et al., A single-cell map of peripheral alterations after FMT treatment in patients with systemic lupus erythematosus, J. Autoimmun. 135 (2023) 102989.
[76] J. Moon, et al., Can gut microbiota affect dry eye syndrome? Int. J. Mol. Sci. 21 (22) (2020).
[77] L. Schaefer, et al., Gut microbiota from sjögren syndrome patients causes decreased T regulatory cells in the lymphoid organs and desiccation-induced corneal barrier disruption in mice, Front. Med. 9 (2022) 852918.
[78] C.S. de Paiva, et al., Altered mucosal microbiome diversity and disease severity in sjögren syndrome, Sci. Rep. 6 (2016) 23561.
[79] R. Mendez, et al., Gut microbial dysbiosis in individuals with Sjögren's syndrome, Microb Cell Fact 19 (1) (2020) 90.
[80] G.L. Wu, et al., Changes of intestinal microecology in patients with primary sjogren's syndrome after therapy of yangyin yiqi huoxue recipe, Chin. J. Integr. Med. 25 (9) (2019) 654–662.
[81] A. Cano-Ortiz, et al., Connection between the gut microbiome, systemic inflammation, gut permeability and FOXP3 expression in patients with primary Sjögren's syndrome, Int. J. Mol. Sci. 21 (22) (2020).
[82] T. Mandl, et al., Severe intestinal dysbiosis is prevalent in primary Sjögren's syndrome and is associated with systemic disease activity, Arthritis Res. Ther. 19 (1) (2017) 237.
[83] C. Wang, et al., Sjögren-like lacrimal keratoconjunctivitis in germ-free mice, Int. J. Mol. Sci. 19 (2) (2018).
[84] M. Zaheer, et al., Protective role of commensal bacteria in Sjögren Syndrome, J. Autoimmun. 93 (2018) 45–56.
[85] A. Watane, et al., Fecal microbial transplant in individuals with immune-mediated dry eye, Am. J. Ophthalmol. 233 (2022) 90–100.
[86] E. Alpsoy, B.C. Bozca, A. Bilgic, Behçet disease: an update for dermatologists, Am. J. Clin. Dermatol. 22 (4) (2021) 477–502.
[87] C. Consolandi, et al., Behçet's syndrome patients exhibit specific microbiome signature, Autoimmun. Rev. 14 (4) (2015) 269–276.
[88] J. Shimizu, et al., Bifidobacteria abundance-featured gut microbiota compositional change in patients with behcet's disease, PLoS One 11 (4) (2016) e0153746.
[89] J. Shimizu, et al., Relative abundance of Megamonas hypermegale and Butyrivibrio species decreased in the intestine and its possible association with the T cell aberration by metabolite alteration in patients with Behcet's disease (210 characters), Clin. Rheumatol. 38 (5) (2019) 1437–1445.
[90] Z. Ye, et al., A metagenomic study of the gut microbiome in Behcet's disease, Microbiome 6 (1) (2018) 135.
[91] N. Oezguen, et al., Microbiota stratification identifies disease-specific alterations in neuro-Behçet's disease and multiple sclerosis, Clin. Exp. Rheumatol. 37 (6) (2019) 58–66. Suppl 121.
[92] T.B. van der Houwen, et al., Behçet's disease under microbiotic surveillance? A combined analysis of two cohorts of Behçet's disease patients, Front. Immunol. 11 (2020) 1192.
[93] D. Tecer, et al., Succinivibrionaceae is dominant family in fecal microbiota of Behçet's Syndrome patients with uveitis, PLoS One 15 (10) (2020) e0241691.
[94] N.S. Yasar Bilge, et al., Intestinal microbiota composition of patients with Behçet's disease: differences between eye, mucocutaneous and vascular involvement. The Rheuma-BIOTA study. Clin Exp Rheumatol 38 (5) (2020) 60–68. Suppl 127.
[95] S.M.S. Islam, et al., Interrelationship of stress, environment, and herpes simplex virus type-1 on Behçet's disease: using a mouse model, Front. Immunol. 12 (2021) 607768.
[96] S.M.S. Islam, et al., Eubacterium rectale attenuates HSV-1 induced systemic inflammation in mice by inhibiting CD83, Front. Immunol. 12 (2021) 712312.
[97] A. Yadegar, et al., Fecal microbiota transplantation: current challenges and future landscapes, Clin. Microbiol. Rev. 37 (2) (2024) e0006022.
[98] G. Ianiro, et al., Variability of strain engraftment and predictability of microbiome composition after fecal microbiota transplantation across different diseases, Nat Med 28 (9) (2022) 1913–1923.
[99] S. Khanna, C.S. Kraft, Fecal microbiota transplantation: tales of caution, Clin. Infect. Dis. 72 (11) (2021) e881–e882.
[100] E.N. Baruch, et al., Fecal microbiota transplant promotes response in immunotherapy-refractory melanoma patients, Science 371 (6529) (2021) 602–609.

Abbreviations

FMT: fecal microbiota transplantation
Tregs: T regulatory cells
AD: atopic dermatitis
SjS: Sjögren's syndrome
AA: alopecia areata
BD: Behçet's disease
TNF: tumor necrosis factor
DMARDs: disease-modifying antirheumatic drugs
JAK: Janus kinase
STAT: signal transducers and activators of transcription
AEs: adverse events
UC: ulcerative colitis
CD: Crohn's disease
FOXP3: forkhead box P3
IBD: inflammatory bowel disease

SCFAs: short-chain fatty acids
Th: T helper
HR: high responding
LR: low responding
IL: interleukin
TNF: tumor necrosis factor
F:B ratio: Firmicutes:Bacteroidetes ratio
DSS: dextran sulfate sodium
HF: hair follicle
SLE: systemic lupus erythematosus
SLEDAI: Systemic Lupus Erythematosus Disease Activity Index
BPB: butyrate-producing bacteri