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Review Article

Gut-skin-axis modulation via fecal microbiome transplant: An ecological approach for atopic dermatitis treatment

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Abstract

There are numerous factors underlying the development and severity of atopic dermatitis (AD) and the skin barrier is central in its pathogenesis. Maintaining a strong skin barrier is principle in the management of AD and this may be achieved via immunomodulation of the skin barrier. Gut-skin-axis has long been established and is cardinal in skin barrier immune regulation. There is a growing body of evidence in the use of fecal microbiome transplant (FMT) to engraft immunomodulating microbiome from healthy persons thus restoring gut microbiome balance. The restoration of microbiome homeostasis leads to the restoration of the systemic and gut-skin-axis immunomodulation. FMT has demonstrated its efficacy in conditions such as recurrent *Clostridium difficile* infection (rCDI), autoimmune disorders, and Chron's disease which is strongly correlated to AD. This paper is made by reviewing publications related to fecal microbiome transplant and atopic dermatitis in order to further elaborate its potential use in the management of AD.

Key words
Atopic dermatitis; Fecal microbiome transplant; Gut microbiome transplant.

Introduction

AD is a chronic remitting inflammatory skin disease with a high prevalence and an increasing incidence in the last century.[1] Epidemiologic studies revealed that moderate AD is common but incidence of severe AD may reach over 50% in several countries and tend to occur in elderly.[2,3] Moderate and severe AD does not respond well to topical therapy and consumption of systemic immunosuppressants is related to numerous side effects.

AD is a complex multifactorial condition and targeting certain underlying pathway may concretely modify the disease course. The gut-skin-axis has been acknowledged to be involved in AD pathogenesis and is pivotal in the maintenance of the skin barrier which is often disrupted in AD patients. Gut microbiome analysis of AD patients revealed a shift in microbiome profile with consequent immune dysregulation leading to disease refractoriness. Restoration of gut microbiome dysbiosis through gut microbiome transplant provides engraftment of functional microbiome and consequently restore the gut microbiome mediated anti-inflammatory substances biosynthesis. It has the potential to surpass existing bacteriotherapy as studies demonstrated the long-lasting engraftment accompanied by great reduction in the colonization of gut pathogens and rapid clinical improvement. This paper is therefore reviewing the potential use of FMT to regain the gut-skinaxis balance for treatment for AD.

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Gut dysbiosis and atopic dermatitis

The gut-skin-axis, an interplay between the gut

microbiome and immune system, is essential in the development cutaneous immunity. This interplay takes place early in life through the stimulation of gut mucosal immune system by intestinal microbiome and leads to the development of T regulator (Treg) cells as well as balanced T helper (Th)1/Th2 function.[4,5] AD is associated with a Th1/Th2 imbalance which generates the secretion of Th2 interleukin such as IL-4, IL-5, and IL-13, elevated production of immunoglobulin E (IgE), and greater binding of *S. aureus* to AD skin.[6]

Prior to the onset of AD, there is a shift in the gut microbiota profile which gives rise to the increased Th2 response.[7,8] These changes are characterized by reduced bacterial diversity[9,10] and more abundance of *Clostridium, Clostridium difficile, Escherichia coli,* and *Staphylococcus aureus* in the gut.[11] Results of a large cohort study revealed that the gut microbiome of infants suffering from AD had a higher colonization of *Escherichia coli* and *Clostridium difficile* than in infants without AD.[12] Both these microbiome induces eosinophilic inflammation and are associated with AD.[13] Although the presence of *S.aureus* strain on the skin induces AD exacerbation, its presence in the gut early in life may promote the maturation of the immune system and is inversely correlated with the incidence of AD.[14,15] Skin barrier of AD patient is further compromised due to gut dysbiosis evoked itch[16] and increased reactivity towards oxidative stress.[17]

Microbiome profile of AD patients also demonstrate a reduced abundance of the genus *Bifidobacterium, Bacteroides, Bacteroidetes* and *Firmicutes*.[11] Presence of the species *Bifidobacterium spp, E coli, C difficile, B fragilis group,* and *Lactobacillus spp* in the gut are known to lower the risk of developing of AD[18,19] *Coprococcus eutactus,* a short-chainfatty-acid (SCFA)-generating microbiome, is also reduced in severe AD.[20] SCFA such as butyrate, propionate, and acetate which are biosynthesized in the gut exerts anti-inflammatory and immunomodulatory properties and is responsible for sustaining the integrity of epithelial barriers.[21] A compromised gut epithelial barrier leads to a "leaky gut" which results in circulation of toxins and gut microorganisms associated with Th2 induced skin inflammation in AD patients.[22,23] Additionally, the gut microbiome regulates the production of linoleic acid and 10-hydroxy-cis-12-octadecenoic acid, substances capable of mitigating AD symptoms.[24]

Fecal microbiome transplant as a novel therapy to restore gut dysbosis

Bacteriotherapy, the administration of commensal bacteria as a mean of therapy, has intensively been investigated and has demonstrated promising results for the management of numerous chronic inflammatory conditions. The reintegration of certain strains of microbiota allows for reconstitution of the microbiome ecology which restores important immunologic functions. There has been numerous studies conducted but the focus of this paper is its role in immunomodulation of AD.

Probiotics is one of the most frequently utilized bacteriotherapy. Consumption of probiotic give rise to a significant colonization of beneficial bacterial strain in the gut which can effectively promote the formation of endogenous barrier, reduce intestinal inflammation, and avoid allergic symptoms.[25] A systematic review showed conflicting results regarding the use of probiotics in AD. Some studies showed that consumption of oral probiotic altered the gut microbiota and lower AD disease severity. Conversely, there are other studies which demonstrated altered gut microbial strain that

was not accompanied by improvement of AD.[10]

Fecal microbiota transplantation (FMT) is a recently developed gut microbiome reconstitution procedure which allows long-lasting reintegration of certain microbiome in the gut, in contrast to probiotics which results in only temporary colonization.[26,27] There are several methods to administer the donor-derived FMT microbial filtrate and oral capsule is a new preparation which offers noninferiority compared to other methods.[28] Manufacturing protocol, efficacy, and safety of oral capsule FMT is further described by *M. Zain et al.* and *Charles Du et al*.[29,30]

FMT has an immunomodulatory action and is an FDA approved treatment of rCDI.[31] It has been vastly investigated for other conditions such as autoimmune disorder, metabolic diseases, and neurologic conditions.[32]

FMT effectively alters the gut microbiome profile and furthermore modulates the immune regulation. Post FMT fecal metabolite investigation of an AD mouse model showed changes in recipient gut microbiome profile, substantially higher SCFA synthesis, and improvement in cytokines profile.[33]

Oral capsule FMT allows alteration of microbiome profile to become similar to that of the donor in adult patients with moderate-severe AD. It has shown a significant correlation between the improvement in SCORAD score and gut microbiome transplant. Some subjects responded immediately after the first FMT while others improved after a few weeks. The transplanted microbial strains gradually become steady, on the other hand pre-existing strain in the recipient are being replaced. Most of the patients maintained clinical improvement during the follow up period but a few patients experienced relapse which responded to another course of FMT.[34]

A mouse model study showed AD clinical improvement and concurrent reduction in IL-4 and IL-13 levels seven days post FMT transplant. Follow up serologic examination revealed low-levels of all inflammatory cytokines with increment of microbiome richness and microbiome profile becoming similar to that of the donor in which there is an increase in the abundance of Firmicutes and decrease in Bacteroidetes forty two days after transplant. There were also improvement in pathways responsible for cell growth and demise, transportation and catabolism; biosynthesis of vitamins, cofactors, energy, amino acid, and glycan; adaptation to environment, and immune regulation post transplantation.[35]

With the administration of FMT, microbial engraftment occurs rapidly with recipient gut microbiome composition resembling that of the donor within 3 days post procedure. This composition was retained until the 4 month follow-up and was accompanied by amelioration of CDI symptoms.[36]

Another long-term follow up of an FMT recipient showed a full and stable engraftment of donor's microbiome with similar profile at phyla level between recipients gut microbiome and the donor at 4.5 years post procedure. Bacterial genera such as Bacteroides, Faecalibacterium, Dialister, and Alistipes which are known to be found in healthy fecal microbiota[37,38] is abundantly detected in both the donor and post FMT recipient. Although the patient demonstrated rapid clinical improvement, observation of the recipient gut microbiota revealed fluctuation in its composition during the first 7 months. Clinical resolution despite microbiome composition fluctuation suggests that microbiome diversity was perhaps already

within the range of the healthy donor, to the extent that clinical resolution had already take place even prior to microbiome stable engraftment. It may also suggests that the gut microbiome transferred had the magnitude to utilize its metabolic role even prior to its stable engraftment.[39]

Study done on animals also demonstrated the efficacy of oral capsule FMT in improving gut microbiome diversity, producing clinical improvement, and increasing skin barrier (higher epidermal hydration and pH) on dogs.[40] Not only does it exhibit clinical improvement, oral capsule FMT also reduces the risk of developing AD on dogs.[41]

How gut microbiome restoration improves atopic dermatitis

Transplantation of the gut microbiome leads to greater alpha diversity with microbiome profile similar to that of the donor within the first week. There was a pronounced transmission and integration of Bacteroidaceae, Lactobacillaceae, Rikenellaceae and Porphyromonadaceae families which are greatly found in the healthy persons and donor. In addition, other families such as Barnesiellaceae, Desulfovibrionaceae, Erysipelotrichaceae, and Odoribacteraceae are also well established. Further analysis also showed an increase in the abundance of Actinobacteria, Bacteroidetes, and Firmicutes which are known have a potential to restore and shift the gut microbiota into a healthy state.[33]

This transplant also generates an abounding amount of SCFA which includes acetic, butyric, isobutyric, and propionic acids. Acetic acid, butyric acid, and propionic acid are the primary product generated from gut microbiota mediated carbohydrate fermentation, and butyric acid, is a metabolite capable of regulating both the activation and apoptosis of immune cells.[22,42] These SCFAs may exert anti-inflammatory effects, has the ability to lower the formation of toxic fermentation compound, improve the ratio of Th1/Th2, elevates the amount of lymphocytes and/or leucocytes in the gut-associated lymphoid tissues, polarize and augment Treg cells, and increase the secretion of gut IgA.[43,44] *Bifidobacterium*, *Lactobacillus*, *Clostridium*,

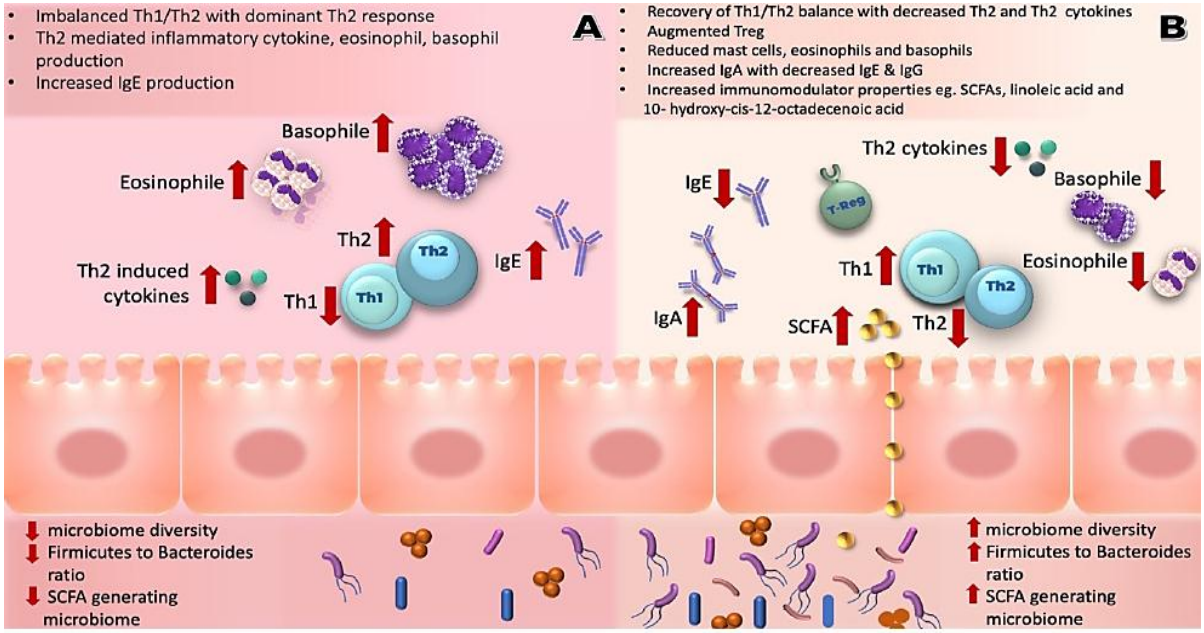

Figure 1: (A) gut dysbiosis impairs microbiome-mediated immunomodulation thus increasing release of proinflammatory substances, (B) post FMT results in gut microbiome reconstitution with in recovery of immunomodulation with increase in anti-inflammatory properties and balanced immune regulation

Kim JE, Kim HS, 2019 [8]

Bacteroides, Streptococcus, and *Akkermansia muciniphila* are examples of the gut microbiome capable of producing such metabolites.[44] *Bacteroides fragilis, Faecalibacterium prausnitzii*, and bacterial species belonging to *Clostridium cluster IV* and *IX* produces retinoic acid and polysaccharide A induces Tregs and lymphocytes which induces anti-inflammatory properties.[22]

The gut microbiome is essential in the differentiation of naive T cells into Th1, Th2, Th17, or Foxp3+ Tregs. Tregs terminates the proliferation of faulty T cells into Th cells and impede inflammatory activities of mast cells, eosinophils and basophils. Th cells also inhibit IgE production and induce IgG4 production.[45] FMT helps regain Th1/Th2 balance via Treg signaling. The concentrations of Th2 cytokines (IL-4, IL-5, and IL-13), which plays a role in the development of AD, were significantly decreased. On the other side, concentrations of Th1 cytokines, such as IL- 12, IFN-γ, and TNF-α were significantly increased. Tregs secreted cytokines (i.e., IL-10 and IL-1β) were significantly lower. Serum levels of IgE and concentration of calprotectin were significantly decreased at the 8th week. This finding is concomitant with significantly lower dermatitis scores.[33] This finding is also in line with a study done on off-spring of mouse models previously given gut microbiota which were then given oxazolone to induce AD. This study found a strong association between gut microbiome, clinical inflammation, and Treg cytokines production by the macrophage (IFN-γ, TNFα, IL-1 β, and IL-6). Off-spring of this mouse models demonstrated gut microbiome profile enriched with Firmicutes and *Lactobacillus* spp and had milder AD upon induction with oxazolone. Fecal gut bacteria donor specimen from a mouse exhibiting high AD response upon oxazolone induction showed a higher abundance of the genus Bacteroides, in which *Bacteroides fragilis* is proven to exert anti-inflammatory and contributes to development of host immunity.[46,47]

The lasting stability of gut microbiome transplantation

There is currently no explanation regarding the mechanism underlying gut microbiome constituent dynamics post procedure. One hypothesis proposed the role of Bacteroides phages derived from donor sample as the gut microbiome regulator. They may exert this dynamic effect through bacterial lysis,[48,49] horizontal gene transfer, and modulation of intestinal immune system[50,51] which depends on Bacteroides as its host.[39]

Results of one study indicates the importance of microbial relative abundance and a higher ratio of donor to recipient relative species abundance in determining the success of microbial transplant in FMT. Microbial investigation in the first week post-transplant was characterized by abundance of both recipient's pre-existent microbiome and the donor transplanted microbiome. Over the subsequent 10-12 weeks, donor microbiome stably persisted while recipient pre-existent microbiome abundance continued to decrease. Datasets presented in this study suggested that gut microbiome genera such as *Bacteroides*, *Blautia*, *Coprococcus* and *Eubacterium* that are persistently identified in healthy individuals are frequently transplanted in rCDI patients in great relative abundance.[52]

On the other hand, there is a study demonstrating correlation between strain persistence and engraftment in which microbiome strains that are persistently found in the gut of healthy persons and donors has a preeminent rate of engraftment in the recipient. Analysis of these microbiome strains showed high ecology competitiveness and fitness which

is pivotal in order to compete against dysbiotic microbiome found in the gut.[53] The importance of strain fitness in gut colonization is also explained by a concept which described the tenacity of *Bacteroides* species as part of the host microbiome, in which the species was acquired by vertical transmission through birth and was persistently found as part of the host microbiome regardless of antibiotic use.[54] Owing to the great influence of the microbiome fitness in the success of transplant, each microbiome capacity to colonize against pathogens found in dysbiotic ecology[55] and endurance against ecological disturbance[56] must be taken into account, perhaps through an ecological identification of fitting microbiome.[57]

A metagenomic gut microbial analysis suggests that microbiome fitness, which is estimated by their widespread presence over the gut, is a better predictor of colonization success compared to microbiome abundance from the donor. This finding demonstrated the potential role of adaptive rather than neutral ecological colonization processes in microbial transplant establishment. High fitness microbiome, which were able to globally colonize the gut, demonstrated a metabolic ability to biosynthesize seven of nine essential amino acids and a higher capacity to biosynthesize cobalamine, riboflavin, and tetrahydrofolate. Further analysis demonstrated that these microbiome are also capable of modulating the bioproduction of pantothenate, thiamine, biotin, and folate[58] which are known to convey host-microbiome interaction.[59] Low fitness microbiome also exert these biosynthesis capacity, although in a rather low magnitude.[58]

Conclusion

Existing studies identified the potential role of FMT in chronic inflammatory cases such as AD. Microbiome transplant via FMT increases microbiome diversity, engraftment of functional microbiome, recovery T cell immunity, and the generation of anti-inflammatory substances. Post-transplantation analysis revealed long-lasting microbiome engraftment concomitant with significant clinical improvement. Animal model studies also showed potential use of FMT as prevention for AD.

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