

Research Progress on the Correlation of Atopic Dermatitis with Gut Microbiota

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Abstract: Atopic dermatitis (AD) is a common skin disease, the pathogenesis of which has not been fully elucidated. The gut microbiota is the largest micro-ecosystem in the human body that affects the immune system and skin barrier function. Recent studies have shown that in addition to the environmental factors, skin barrier, genetic factors and immune response, gut microbiota disturbance may also cause AD. This review described the correlation of AD with gut microbiota and existing research status of AD treatment via targeting gut microbiota.

Keywords: atopic dermatitis, gut microbiota, fecal microbiota transplantation

Introduction

Mediated by the immune system, atopic dermatitis (AD) is a chronic, recurrent, inflammatory skin disease caused by both genetic and environmental factors. It is clinically characterized by dry skin and severe itching.¹ AD can be divided into acute phase and chronic phase according to the course of the disease. Clinical manifestations of acute phase of AD include severe erythema, papules, exudation, and severe itching, and those of the chronic phase include dry skin with scales, and dermatoglyphic patterns with lichenoid manifestations. The incidence of AD has gradually increased with the development of industrialization and urbanization. Epidemiological data revealed that globally, 15–30% of children and 10% of adults have a history of AD. It is estimated that there were 390 million AD patients worldwide in 2019, which is expected to reach 450 million by 2024 and 520 million by 2030, involving more than 33.3% moderate-to-severe cases. Besides skin lesions, AD also increases the risk of cardiovascular events like atrial fibrillation.² AD brings a heavy financial burden to affected patients. The mean annual treatment cost per AD patient is as high as 40,000 yuan. In addition, AD patients may also suffer from severe mental disorders like anxiety, depression or even suicidal tendencies.³ Therefore, the pathogenesis and therapeutic strategies for AD have been widely explored, serving as a hotspot in the field of dermatology.

It is generally believed that immune abnormalities and skin barrier damage are the most important causes of AD. However, in recent years, a growing number of evidences have shown that changes in the gut microbiota can lead to abnormal immune responses, thereby causing skin inflammation. It may be one of the potential pathogenetic causes of AD. The human intestine has a total length of 7–8 m and a surface area of about 200 m², storing 90% of the human microbiome. Gut microbiota participates in important biological events like metabolism, immune regulation, and nerve signal transduction. Their composition and structure are closely related to human health. Gut microbiota is vital in environmental factors, and the gut microbiota disturbance is closely linked with chronic diseases, including skin diseases (eg, acne, psoriasis, etc).⁴ Therefore, maintaining a good symbiotic relationship between the human body and gut microbiota favors human health.

Recent studies have shown that gut microbiota participates in the regulatory process of the immune system, which is closely related to the occurrence and development of AD. It is generally believed that AD is caused by abnormalities in the immune system, especially the dysregulation of Th2 inflammatory response. The diversity and stability of gut microbiota are subsequently damaged, leading to decreased abundances of beneficial gut bacteria and increased

abundances of opportunistic pathogenic gut bacteria.⁵ Therefore, it is of great significance to illustrate the changes in the gut microbiota in AD patients, and the pathogenesis of gut microbiota involved in the development and progression of AD, thus providing theoretical references for AD treatment targeting gut microbiota.

Overview of AD and Gut Microbiota

Classification of Gut Microbiota

Massive microorganisms parasitize the human intestine, including bacteria, archaea, fungi and viruses, constituting a microbiome. Bacteria are the predominant composition of the microbiome. A total of 10^{14} bacteria parasitized in the human intestine, weighing 1–1.5 kg, the number of which is 10 times the total number of human cells. The total number of gut microbiota is about 100 times that of the human genome, and more than 99% of them are the *Firmicutes*, *Bacteroidetes*, *Proteobacteria* and *Actinobacteria*. Among them, the *Bacteroidetes* and *Firmicutes* dominate the gut microbiota in healthy adults. The abundance of each type of bacterium varies a lot, but more than 99% of the total number of bacteria is composed of 30–40 species of bacteria. According to their functions, they are classified into beneficial bacteria, harmful bacteria and opportunistic pathogenic bacteria, and most of them are the *Firmicutes* and *Bacteroidetes*, with a small proportion of others.⁶

Changes in the Gut Microbiota of AD Patients

At present, changes in the gut microbiota of AD patients remain controversial, with varied relative abundances of gut bacteria. The diversity of gut microbiota promotes the occurrence of AD, but others also proposed that AD is able to affect infants with a low diversity of gut microbiota.⁷ Geographic location is another important factor affecting gut microbiota. For example, children from the Northeast Thailand have greater abundances of *Bacteroides fragilis*, *Clostridium leptum*, *Prevotella*, *Clostridium coccoides*, *Eubacterium rectale*, and *Lactobacilli* than those from the central Thailand.⁸

Epidemiological data showed the increased proportions of *Clostridium difficile*, *Escherichia coli*, and *Staphylococcus aureus*, and decreased proportions of *Bifidobacterium* and *Bacteroidetes* in the gut microbiota of AD patients. The composition of gut microbiota in AD patients differs from that of healthy people, manifesting as decreased abundances and activities of *Lactobacilli* and *Bifidobacteria*.⁹ Yongbo et al¹⁰ conducted a two-sample Mendelian randomization to identify the correlation between gut microbiota and AD. They suggested that the proportions of the *Dialister* and *Prevotella* decreased in gut microbiota of AD patients. It is reported that the proportions of the *Clostridium*, *Clostridium difficile*, *Escherichia coli* and *Staphylococcus aureus* in the gut microbiota of AD patients are significantly higher than those of healthy volunteers, while those of *Bifidobacteria*, *Bacteroidetes* and *Bacteroidetes* are lower.¹¹

Wu et al¹² analyzed the gut microbiota in infants with AD from Northeast China. They found that *Bifidobacteria* and *Bacteroidetes* are both enriched in the intestine of healthy infants and those with AD. Sung et al¹³ analyzed gut microbiota in mothers with AD and their infants. The relative abundance of *Proteobacteria* is significantly higher in the gut microbiota of mothers with AD than that of healthy volunteers, while the *Verrucomicrobia* is only detectable in the intestine of the latter group. Moreover, the abundances of *Bifidobacterium*, *Bifidobacterium Breve*, *Paratrophic Clostridium*, *uncultured Clostridium*, *uncultured Trichobacteriaceae* and *Lactobacillus* are significantly lower in the gut microbiota of infants with AD than those of healthy infants, while those of *Bacteroides*, *Dorea longicatena*, *Faecalibacterium* and *Ruminococcus lactaris* are significantly higher. Melli et al⁹ reported that compared with those of healthy children, significantly higher abundances of *Clostridium difficile* and *Bifidobacterium* and lower abundance of *Lactobacillus* are detected in the gut microbiota of children with AD. Meanwhile, there are significant differences in the abundances of *Escherichia coli*, *Bacteroides fragilis*, and *Methanobrevibacter smithii* in the gut microbiota between healthy children and children with AD. Liu et al¹⁴ revealed that the diversity of gut microbiota decreases in AD patients than that of healthy people. In adults with AD, the abundances of *Agathobacter* and *Dorea* significantly decrease, and that of *Bacteroides pectinophilus* increases.

The Involvement of Gut Microbiota in AD

The gut microbiota disturbance destroys the diversity and stability, leading to immune dysfunction and thus causing the development of AD. The reduction of probiotics or the elevation of harmful and opportunistic pathogenic bacteria results in the gut microbiota disturbance. The subsequent changes in the gut microbiota metabolism and immune response ultimately cause AD. In addition, the hygiene hypothesis proposed that the reduced exposure to commensal and pathogenic microorganisms in early childhood may result in insufficient stimulation and maturation of the immune system. As a result, the gut microbiota dysbiosis is a fundamental cause of the increased prevalence of AD. Some bacteria like *Bifidobacterium* and *Lactobacillus* are able to attenuate allergic reactions and promote the production of anti-inflammatory cytokines like IL-10 via stimulating regulatory T cells. Therefore, the gut microbiota exerts an important role in maintaining immune homeostasis.¹⁵

Compared with that of healthy volunteers, the diversity of skin and gut microbiota decreases before the onset of AD in children, leading to the changes in Th2 response and the increased susceptibility to AD. *Lactobacilli* and *Clostridium* are dominant bacteria in the gut microbiota of children from Estonia and Sweden, respectively. Swedish children suffer a high incidence of allergies than that of Estonian children.¹⁶ In vitro and in vivo studies have validated the regulatory effects of *Lactobacillus* on the immune system and against allergies. Compared with non-allergic individuals, allergic infants have a lower abundance of *Lactobacilli* and higher abundances of aerobic bacteria in the intestine. Children with lower abundances of *Bifidobacteria*, Gram-positive aerobic bacteria, and *Enterococci* are less likely to have allergies, but those with high abundances of *Clostridium* and *Staphylococcus aureus* are prone to allergic symptoms.¹⁷

A series of rodent and human studies have demonstrated the importance of gut microbiota in maintaining the health and appearance of the skin. Levkovich et al¹⁸ reported that mice supplemented with *Lactobacillus* have thicker and shinier skin and increased density of hair follicles and sebaceous glands. Horii et al¹⁹ illustrated that oral supplementation of *Lactobacillus brevis* SBC8803 in rats increases the release of serotonin from enterochromaffin cells, which subsequently activates the parasympathetic pathway, thereby reducing cutaneous arterial sympathetic tone, increasing cutaneous blood flow and lowering transepidermal water loss (TEWL). Ogawa et al²⁰ revealed that TEWL is significantly reduced and corneal hydration is significantly promoted in humans after 12 weeks of oral supplementation of *Lactobacillus brevis* SBC8803. Benyacoub et al²¹ suggested that the decreased sensitivity in the skin and TEWL after 2 months of supplementation of *Lactobacillus paracasei* NCC 2461 can be attributed to the enhanced skin barrier integrity via upregulating TGF- β .

Baba et al²² identified that the induction of *Lactobacillus helveticus*-fermented milk whey in human epidermal keratinocytes upregulates keratin 10 and trichogin, which are the biomarkers for early-stage and advanced differentiation. It is suggested that *Lactobacillus helveticus* promotes epidermal differentiation. Furthermore, polyprotein is dose-dependently upregulated and it is eventually cleaved to form filaggrin (FLG), which is a protein critical for epidermal flexibility and hydration. Therefore, *Lactobacillus helveticus* has a potential moisturizing effect.

Communication between the gut and skin relies on the activity of immune components, and regulating host-microbiota interactions is a fundamental function of the immune system. The areas where symbiotic organisms are colonized, like the skin and gastrointestinal tract, contain a large number of immune cells. The dominant role of the symbiotic microbial community in regulating the immune system contributes to enhance the barrier immunity, balance the microecological stability and alleviate inflammatory responses.

Prevention and Management of AD via Targeting the Gut Microbiota

According to the Chinese Guidelines for the Diagnosis and Management of Atopic Dermatitis, a de-escalation therapy is adopted. Basic treatment is first applied to AD patients, including health education of searching and avoiding triggering factors and the use of moisturizing lotions. Topical treatment is applied to mild AD patients, including topical corticosteroids (TCS), topical calcineurin inhibitors (TCI) or phosphodiesterase 4 (PDE-4) inhibitors.²³ Moderate-to-severe AD patients are additionally given to systematic treatment or phototherapy. Systematic treatment drugs include immunosuppressants (eg, cyclosporine, methotrexate, azathioprine, mycophenolate mofetil) and traditional Chinese herbal medicines (eg, tripterygium wilfordii, compound glycyrrhizic acid). However, their long-term efficacy on AD is unclear, and the long-term medication is limited by the risk of organ toxicity and malignancy.²⁴ Dupilumab, which was launched in China in 2020, has achieved significant outcomes in moderate-to-severe AD, but its applicability as a routine

treatment is controversial. The regulation of gut microbiota, as a result, provides a safe and innovative option for the treatment of AD by posing a positive impact on the skin.

Regulation of Intestinal Contents of Short-Chain Fatty Acids (SCFAs)

Short-chain fatty acids (SCFAs) are metabolites produced by intestinal beneficial bacteria in metabolizing carbohydrates like the dietary fiber. The most common SCFAs include acetic acid, propionic acid, and butyric acid.²⁵ Clinical studies have shown that SCFAs can maintain the morphology and function of the intestine, exerting therapeutic effects. Regulating SCFAs in the human intestine may be an important therapeutic strategy for AD. The supplementary of beneficial bacteria that produce butyric acid or acetic acid can effectively prevent and control AD. Canfora et al²⁶ found that the intracolonic injection of a mixture of SCFAs promotes energy metabolism in overweight or obese men. Notably, dietary fiber favors the production of SCFAs by the gut microbiota, which is conducive to alleviate AD. However, the regulatory effect of dietary fibers on the gut microbiota differs a lot, and in turn, individualized difference in the composition of gut microbiota causes different responses to dietary fiber intervention. A blind supplementary of SCFAs by increasing dietary fiber intake may not achieve the desired outcome. An individualized diet adjustment plan is made after identifying the composition and abundances of gut microbiota.

Regulation of Probiotics and Prebiotics

Probiotics are live microorganisms that colonize the intestine in the host. They are indispensable elements for human health via synthesizing multiple vitamins, participating in food digestion, promoting intestinal peristalsis, inhibiting the growth of pathogenic bacteria, and decomposing toxic substances.²⁷ Probiotics contribute to maintain the microbial balance, showing the immune regulation, anti-oxidation and anti-inflammation properties. The Th2 response is a typical characteristic of AD. Oral supplementary of probiotics inhibits the Th2 response and induces the Th1 response. Moreover, it induces immune tolerance and maintains Th1/Th2 balance, thereby achieving the therapeutic outcome of AD. It is found that oral probiotics can reduce abnormal colonization of bacteria like *Staphylococcus aureus*, restore the diversity of gut microbiota and the intestinal barrier function, thereafter alleviating the clinical symptoms of AD.

Ahn et al²⁸ found that oral administration of *Ruminococcus gnavus* significantly reduces AD-associated indexes, including TEWL, clinical scores, total IgE level and specific IgE level, which also significantly downregulates mRNA levels of helper T cell-associated cytokines in the skin and IL-10, and upregulates Foxp3. Increased number of CD4⁺FOXP3⁺ T cells in mesenteric and cutaneous lymph nodes and butyrate levels in the cecum are found in AD mice supplemented with probiotics. Fang et al²⁹ demonstrated that *Lactobacillus reuteri* DYN DL22M62 significantly alleviates clinical symptoms of AD mice by inhibiting IgE level and expression levels of TSLP, IL-4 and IL-5. The *Lactobacillus reuteri* DYN DL22M62 increases the production of indole lactic acid (ILA) and indole propionic acid (IPA) in mice by targeting the tryptophan metabolism and AHR expression. In addition, it increases the proportion of *Romboutsia* and *Ruminococcaceae* NK4A214 (a positive correlation with ILA) and decreases that of *Dubosiella* (a negative correlation with IPA). Overall, *Lactobacillus reuteri* DYN DL22M62 regulates the gut microbiota, production of indole derivatives and activation of AHR in mice, thus alleviating AD.

Gut microbiota disturbance in AD patients leads to decreased number of probiotics, and therefore, adjusting probiotics can effectively alleviate symptoms of AD. Michelotti et al³⁰ showed that the 1-month treatment of *Lactobacilli* mixture in AD patients improves skin smoothness, skin moisturizing, and self-perception and reduces the SCORing Atopic Dermatitis (SCORAD) index and AD-associated inflammatory markers. Prakoeswa et al³¹ reported that after the 12-week treatment of *Lactobacillus plantarum* IS-10506 and CJLP133 in children with AD, they observed significant improvement of symptoms of AD, lower SCORAD than that of placebo group and no obvious adverse events. Moreover, oral probiotics provide a better therapeutic outcome of children with AD who have increased total IgE. Navarro-López et al³² revealed that oral probiotics are more effective in children with AD over 1-year old, and the efficacy is more pronounced in moderate-to-severe cases than that of mild cases. In addition, multi-strain preparations, especially probiotic mixtures containing *Lactobacilli* and *Bifidobacteria*, have a better therapeutic effect than that of single-strain preparations. A randomized clinical trial showed that both single-strain preparations and multi-strain mixed probiotic preparations can effectively alleviate the clinical symptoms of AD in children, which is more pronounced in the

latter.³³ Oral administration of a single-strain *Lactobacillus acidophilus* or a mixture of *Lactobacillus acidophilus* and other probiotics can alleviate the clinical symptoms of children with AD. The combination supplementary of *Lactobacillus casei* and *Lactobacillus salivarius* reduces IgE level in children with AD.

Accumulating evidences have shown the benefits of probiotics for AD, particularly in pregnant women, newborns and infants. A combination supplementary of *Lactobacillus rhamnosus* (LGG) and *Bifidobacterium animalis* (BB-12) to children in late infancy (8–14 months) before attending daycare institutions prevents AD, although it does not provide benefits to prevent other allergic diseases or food allergies. In 2020, a meta-analysis reported that oral probiotics effectively lower the prevalence of AD in pregnant women and newborns.²⁷

Prebiotics are defined as non-digestible food ingredients that promote the growth of certain bacteria in the intestines. Some common prebiotics include galacto-oligosaccharides (GOS) and fructo-oligosaccharides (FOS). A supplementary of GOS, inulin, and pectin to the diet of 1-year-old infants with low-risk AD has a preventive effect on AD, which is similar to that of probiotics. Prebiotics may provide health benefits to the skin, including the increase in skin hydration and decreases in urinary and serum phenols produced by intestinal bacteria.³⁴ Unlike probiotics, prebiotics have been less analyzed, although they are promising elements.

Fecal Microbiota Transplantation

Fecal microbiota transplantation (FMT) is a method of reshaping gut microbiota, which is a vital therapeutic strategy for gut microbiota-induced disorders. Briefly, intestinal probiotics are transplanted from healthy volunteers to receptors with gut microbiota disturbance, thus yielding the microecological balance in the rebuilt gut microbiota. FMT contributes to the treatment of intestinal and extraintestinal diseases, which has been hailed by the *Time* magazine as one of the Top Ten Medical Breakthroughs in 2013. It is now applied to the treatment of diarrhea, constipation, diabetes, obesity, skin allergic diseases, intestinal allergic diseases, neurodevelopmental abnormalities, and neurodegenerative diseases.³⁵

Kim et al³⁶ revealed that FMT restores the gut microbiota of receptor mice similar to that of donor mice, which increases the content of intestinal SCFAs. In addition, FMT regulates Tregs, lowers IgE level and the number of mast cells, eosinophils, and basophils, and restores the Th1/Th2 balance, serving as a potentially novel AD treatment. So far, thousands of patients around the world have received FMT. It has also applied to AD patients by transplanting fecal bacteria from healthy volunteers, which effectively alleviates clinical symptoms and stabilizing IgE level.

With the in-depth research on the microbiota-gut-brain axis, gut microbiota has been found to influence emotions of AD patients via a close link with itching, especially the neuroregulation. Therefore, FMT may be a potential treatment of AD. Mashiah et al³⁷ reported that FMT effectively stabilizes the disease condition in 9 AD patients. In the future, FMT may become an important therapeutic strategy for AD.

Others

Previous studies have confirmed the close correlation of gut microbiota with the systemic chronic inflammatory response. Oral antibiotics alleviate clinical symptoms of AD by regulating the gut microbiota.³⁸ Notably, oral antibiotics can also damage probiotics, leading to the gut microbiota disturbance and subsequent negative influences. Abuse or blind use of antibiotics is not recommended during the treatment of AD. An individualized thorough treatment regimen should be made by fully considering the cause and condition of AD.

Summary and Outlook

Accumulating evidences have shown the close correlation between the composition of gut microbiota and AD. A balanced gut microbiota contributes to the acceleration of metabolism and the improvement of immune function. The regulation of gut microbiota is capable of improving the intestinal immune system, thereafter alleviating clinical symptoms of AD.

Previous studies, however, have not summarized the treatment of AD via targeting the gut microbiota. This review mainly focused on the correlation of gut microbiota with AD, and its treatment via regulating gut microbiota, thus providing theoretical guidance for clinical management of AD.

In the future, non-invasive diagnosis of early-stage AD by detecting biomarkers like SCFA contents in feces and serum levels of relevant amino acids and regulation of the gut microbiota composition by drugs are major research directions of

innovative treatment of AD. So far, clinical efficacy of existing drugs for AD is limited and they cause adverse events. We believed that effective and safe therapeutic strategies for AD by regulating gut microbiota will be developed.

Disclosure

The authors report no conflicts of interest in this work.

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