EAAS 2: Microbiome in allergic diseases

Dysbiosis in the Human Microbiome Underlying Atopic Dermatitis

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Introduction

The microbiome is the genetic material of all microbes that live on or in the human body. Humans are sterile during gestation. Exposures in early life result in colonization of gut and skin microbiota which contributes to the development of the immune system, homeostasis and host metabolism. The microbiome is essential for human development, immunity, and nutrition. However, altered composition and diversity of microbiota is characterized of various allergic diseases including atopic dermatitis (AD).

1. Development of gut and skin microbiome

The gut microbiome harbours the largest pool of foreign antigens, with 100 trillion resident bacteria. Postnatal microbial colonization of the gut and skin occurs in the early neonatal period. Exposure in early life mode of delivery, infant diet, probiotics and physical environment results in colonization of gut microbiota which contributes to the development of the immune system. The intestinal commensal bacteria play diverse functions including protective barrier against bacteria or pathogens, structural function and regulating nutrient metabolism including absorption of indigestible carbohydrate and production of short chain fatty acid (SCFA). Gut colonization by beneficial organisms could confer protection against atopy, with repeated early exposure to particular groups of bacterial antigens enhancing immune regulation and development. Skin microbiome able to be affected by lifestyle, age, diet, genetics, drugs or hygiene products. *Staphylococcus aureus* (*S. aureus*) had a high prevalence on the skin of AD patients. Normal skin from controls was in contrast colonized by coagulase-negative *Staphylococcus epidermidis* (*S. epidermidis*), followed by *S. aureus*, micrococci and lipophilic diphtheroides. *S. aureus* counts correlated with disease severity, while a reverse tendency was seen for *S. epidermidis*.

2. Dysbiosis of gut microbiome in AD

AD is a common chronic skin disease in children. Improved hygiene and decreased exposure of the immune system to microorganisms in infants are considered to be possible environmental etiologies of AD. The intestinal microbiota is thought to play an important role in the pathogenesis of AD. Using cultivation methods, there were only trends for early gut colonization of *S. aureus* and *Bacteroides* and later development of AD. With culture-independent molecular methods, AD development was associated with reduced bacterial diversity in the gut. However, not all studies associated low gut microbiota diversity with AD development.

Dysbiosis is defined as qualitative and quantitative changes in the intestinal flora. Modern diet such as high fat, high-sugar diet, over nutrition and lifestyle, antibiotics, psychological and physical stress result in overgrowth of potentially pathogenic microorganisms and alterations in bacterial metabolism. Numerous studies have confirmed the differences in gut microbiota between those with AD and controls. The gut microbiota composition of AD patients shows an imbalance of microbial species, particularly showing a low number of *Bifidobacteria/Lactobacilli* and a high level of *Clostridia*, *Staphylococci*, and *Escherichia coli*. In addition to quantitative differences in the specific species, low total diversity of gut microbiome has also been observed in patients with AD. Several studies have found that reduced gut microbial diversity in infancy is associated with an increased risk of allergic diseases in school-aged children. On the other hands, sub-species level dysbiosis of specific microorganism (*Faecalibacterium prausnitzii*) has been reported to be associated with AD.

3. Dysbiosis of skin microbiome in AD

Studies of skin microbiome demonstrated that *S. aureus* abundance fluctuates and parallels clinical symptoms in AD. *S. aureus* was enriched on the skin of AD patients compared to healthy controls and correlated with disease severity. *S. aureus* was found more from the affected than the unaffected skin in patients with AD. During an untreated flare of AD, the skin microbiota in lesion areas is represented to over 90% by *S. aureus*, while rare on control skin. Moreover, the increase in the proportion of *S. aureus* on the skin and the decrease in microbial diversity did not only correlate with the clinical score, but actually preceded the worsening of AD disease severity.

Interventions with the antibiotics in AD patients, who were heavily colonized with *S. aureus*, resulted not only in a reduced colonization but also in a reduction of clinical severity. Moreover, corticosteroid or emollient treatment in AD patients observed reduction of clinical severity with a reduction in *S. aureus* colonization. Various treatments reducing *S. aureus* skin load also reducing AD symptoms, suggesting *S. aureus* as a potential critical driver of AD and a target for antimicrobial interventions other than antibiotics. The majority of the AD patients were colonized with super antigen (SAg) producing *S. aureus* which

correlated with a higher total IgE titer. Researchers showed a correlation between the detection of *S. aureus* SAg and severity score and serum IL-4 levels. In another study, the most of the AD patients who were colonized with *S. aureus* produced α-toxin, which was correlated with a higher total IgE levels. It seems that AD is not any longer a disease of altered skin barrier and immune dysfunction, but also a disease of skin microbiota dysbiosis with *S. aureus.*

4. Microbiota-immune interactions

Crosstalk between gut flora and the immune system stimulates the development of gut mucosal immunity. The balance between immune tolerance and inflammation is regulated in part by the crosstalk between innate and adaptive immune cells and the intestinal microbiota. Disrupted communication between the microbiome and the host due to altered microbiome composition and/or metabolism is thought to negatively influence intestinal immune homeostatic networks. Mucosal diversity is crucial for development of an immune-regulatory network that protects against induction of IgE synthesis by the mucosa. Imbalances in the composition of the intestinal microbiota may trigger allergic disease.

Regarding to possible mechanisms relating immune responses, some commensal microbes and metabolites in the gut are known to induce regulatory T (Treg) cells. The Foxp3+Treg is characterized by the production of IL-10, one of the major immune-regulatory cytokines, and considered to suppress the excessive activation of Th2 cells thereby ameliorating allergic responses. The gut microbiota also induce B cell maturation and cause such cells to switch their immunoglobulin isotypes. A preference for IgE tends to activate basophils and mast cells, in turn modifying the microbiota. SCFAs produced upon fermentation of dietary fibers by intestinal bacteria may be involved in regulation of both local and systemic allergic inflammatory responses, too. SCFAs can modulate epithelial barrier function, production of antimicrobial peptides, and secretion of pro-inflammatory mediators.

There are plausible mechanisms of gut bacterial manipulation and reduction in AD risk. Probiotics may improve health by modulating local immunity, maintaining gut wall integrity, stimulating systemic immunity, or enhancing immune system. Administration of probiotics may restore the immune tolerance by diverse mechanisms such as enforcement of barrier function of gut epithelial cells, restoration of gut microbiota composition and phenotypic alteration of immune cells. It could restore Th1/Th2 balance by producing immune-modulatory cytokines such as IL-10, TGF-ß and IgA and, generate CD4+Foxp3+ Tregs which could suppress diverse immune disorders. Orally administered probiotics could interact with gastrointestinal mucosa and gut associated lymphoid tissue (GALT). Probiotics also interact with intestinal epithelial cells (IECs), mucosal dendritic cells (DCs) and macrophages through diverse way. Toll-like receptors and DCs in lamina propria induce immune activation signaling and trigger tolerance signaling. Therefore, probiotics may act against the inflammatory process, through above-mentioned mechanisms as promoting the antigen's exclusion, enhancing the enteral antigens degradation, altering their immunogenicity and thus reducing antigen level.

The presence of appropriate commensal organisms have been purported to help establish the Th1/Th2 balance of the developing immune system. Together, it has been suggested that modulating gut bacteria may protect against the development of AD.

In patients with AD, dysbiosis of skin microbiome was observed, too. Studies in skin samples of AD patients have shown that outgrowths of *S. aureus* species correlate with disease flares, with associated reduction in the overall diversity of microbial communities in the skin. Following antimicrobial therapy, a reduction in severity of symptoms was linked with a return of normal commensal bacteria species to the skin suggestive of a role for bacterial diversity in regulating skin inflammation.

Conclusions

High-performance new techniques has opened new avenues for better understanding of microbiota compositions, activities, and interactions with probiotics. Culturomics have a role in the full description of the gut microbiota. The metagenomics sequencing particularly the NGS technologies can overcome many of the culture-based limits. Proteomics studies provide fingerprinting profiles related to peptidome and proteome, detecting the protein patterns expressed in the gut microbiota ecosystems. Very recently, metabolomics strategies allow reaching high throughput, sensitivity, resolution, and the ability to identify and quantify a wide number of molecules by different platforms. Generation of omics-based charts can substantially support the interpretation of gut microbiota dysbiosis and gain further functional information. Understanding the complex interactions of the human microbiome will aid the development of novel and more targeted treatments to modulate the microbiome and influence AD outcomes.

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