

Microbiome in atopic dermatitis

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Abstract: Atopic dermatitis (AD) is a common chronic inflammatory skin disease affecting ~10–20% of the general population. AD is characterized by disturbances in epidermal barrier function and hyperactive immune response. Recently, changes in the skin and intestinal microbiome have been analyzed in more detail. The available data suggest a link between disturbed skin microbiome and course of the disease. Flares of the disease are associated with an expansion of *Staphylococcus aureus* on lesional skin and a substantial loss of biodiversity in skin microbiome. *Staphylococci* exoproteins and superantigens evoke inflammatory reactions in the host. Skin microbiome includes superficial stratum corneum that is affected by environmental factors such as exposure to germs and cleansing. Available evidence argues for a link between epidermal barrier impairment and disturbances in skin microbiome in AD. In contrast to skin microbiome, intestinal microbiome seems to become stabilized after infancy. There is also a significant heritable component for intestinal microbiome. The microbial taxa, relative percentages and quantities vary remarkably between the different parts of the intestinal tract. Early intestinal microbial colonization may be a critical step for prevention of further development of AD. Skin barrier-aimed topical treatments help to develop a neo-microbiome from deeper compartments. Probiotics, prebiotics and synbiotics have been investigated for the treatment of AD, but further investigations are needed. Targeted treatment options to normalize skin and intestinal microbiome in AD are under investigation.

Keywords: atopic dermatitis, microbiome, staphylococci, skin, intestine, antimicrobial peptides

Introduction

On skin and mucous membranes (intestine, airways), microbial genomes outnumber those of the human host by a factor of 100. The microbiome (microbiota), i.e., the bacteria, viruses, archaea and fungi, living on and within the human body contributes to health and disease. The microbiome is individual and changes with age. The crosstalk between the microbiome and the human host is realized by secretion of metabolites from microbes and the human immune system scanning the microbiome for information about metabolic state and colonization. Thereby, bacteria-derived molecules such as short-chain fatty acids may influence human epigenomic pathways.^{1,2} This article reviews the role of the human microbiome in atopic dermatitis (AD).

AD

AD is a common chronic inflammatory skin disease affecting ~20% of children. In 95% of cases, initial manifestation of AD occurs within the first 5 years of life.

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Approximately a quarter of these children continue to have AD during adulthood.³

In the pre-school age, 30% of children with AD suffer from food allergies (eggs, cow's milk, peanuts). Those with moderate to severe AD have a 50% risk of developing asthma and 75% risk of developing hay fever.^{4,5}

AD diagnosis is made by almost exclusively clinical criteria.⁶⁻⁸ Genetic and epigenetic factors modulate AD. Environmental factors such as (perinatal) exposure to indoor and outdoor allergens and pollutants, nutrition and microbiome are considered as influential for the manifestation and severity of AD. Environmental factors regulate gene expression through microRNA (miR) and genomic DNA modification. Among genetic factors, filaggrin (FLG) null gene mutations are the most significant risk factor for AD. Furthermore, genes in T helper lymphocyte type 2 (Th2) signaling pathways represent a second important genetic risk factor for AD, although predominant Th2 response is limited to the flare-ups. Genome-wide association studies have identified >30 risk loci for AD for genes involved in epidermal barrier function and immune response. Gene profiling assays revealed overexpression of Th2, Th17 and miR-155.^{9,10}

Epigenetic studies in AD have demonstrated significant changes in the methylation status of skin lesions, e.g., hypomethylation of gene promoters and alterations in miR profile.¹¹⁻¹³ Genetic and epigenetic studies suggest that two major pathways are involved in AD, i.e., innate and adaptive immune systems and epidermal barrier function.⁹⁻¹³

Levels of the antimicrobial metabolite sphingosine and antimicrobial peptides cathelicidin and defensins B2 and B3 are reduced in the skin of AD subjects.¹⁴ These factors contribute to the increased risk of cutaneous infections in AD.

Cutaneous microbiome and AD

Resident skin bacteria are influenced by topological and endogenous factors of skin and can be modulated by external factors such as clothing, hygiene, topical treatments and skin care products (Table 1). There are gender differences in skin microbiome as well. Skin microbiomes differ between children and adults (described in the following). Bacteria are not uniformly distributed in skin. There is a superficial and a deeper compartment in the human stratum corneum. After injury, a neo-microbiome is produced from the deeper compartment, which can be regarded as the indigenous microbiome. Furthermore, bacteria are consistently detectable also in deeper skin layers such as the dermis and the subcutaneous adipose tissue. A balanced resident skin flora is a protective measure.^{15,16}

Table 1 Normal human skin microbiome^a

Skin type	Normal microbiome (most abundant bacterial groups)
Sebaceous skin	<i>Propionibacteria</i> spp., <i>Corynebacteria</i> spp., other <i>Actinobacteriales</i> spp., <i>Staphylococci</i> spp.
Moist skin	<i>Corynebacteria</i> spp., <i>Staphylococci</i> spp., β - <i>Proteobacteria</i> , γ - <i>Proteobacteria</i>
Dry skin	β - <i>Proteobacteria</i> , <i>Corynebacteria</i> spp., <i>Flavobacteriales</i>

Note: ^aAccording to Costello et al.³²

Among the Gram-positive *Staphylococcus* species, *Staphylococcus epidermidis* is the dominant type in healthy skin with the ability to inhibit the growth of *Staphylococcus aureus*.¹⁷ In children, colonization of skin by *S. epidermidis* and *S. cohnii* during the first year of life has a protective effect on the development of AD.¹⁸

Disturbances in cutaneous microbiome represent an independent risk factor for the development of AD. In ~90% of patients suffering from AD, the skin becomes colonized by *S. aureus* of which 50% are toxin producing. These toxins can contribute to inflammation and skin barrier dysfunction via activating the host inflammasomes.¹⁹

Using whole metagenome profiling, distinct signatures enriched for *Streptococcus* and *Gemella* but depleted for *Demacoccus* were identified in subjects prone to AD. This was accompanied by changes in the innate and Th1 adaptive immune responses to *S. epidermidis* and *S. aureus*.²⁰

In lesional AD, however, the proportions of both *S. aureus* and *S. epidermidis* increase. Since these species produce antibacterial compounds such as antimicrobial peptides and bacteriocins, a relative decrease in other species, including *Propionibacterium*, *Corynebacterium* and *Streptococcus*, occurs during AD flares. After successful topical AD treatment, there is an increasing biodiversity of cutaneous microbiome that arises from taxa already present in cutaneous microbiome.^{21,22}

In AD, *S. aureus* is capable of inducing flares of the disease. There is an increased colonization of lesional skin in AD patients. Membrane vesicles released from these bacteria can penetrate the epidermis and induce a massive infiltration of inflammatory cells with a mixed Th1/Th2 immune response.²³ *S. aureus* itself is capable of penetrating the epidermis in case of increased cathelicidin expression and increased expression of interleukin (IL)-4, IL-13, IL-22, and other cytokines.²⁴ *S. aureus* can directly impair skin barrier function by stimulating the production of keratinocyte endogenous serine protease. This diminishes FLG and other epidermal proteins and contributes to disturbed lipid lamellar function.²⁵ *S. aureus*-associated, microbial-associated molecular patterns bind to

Toll-like receptor 2 (TLR2) heterodimers and induce long-lasting and self-perpetuating T-cell inflammation.²⁶

On the other hand, AD is a risk factor for colonization of nasal mucous membranes and the skin by methicillin-resistant *S. aureus* (MRSA).²⁷ MRSA prevalence on lesional skin has been reported from 13 to 24%.^{28,29} This can cause recurrent MRSA infections in patients with AD.³⁰

Staphylococcus epidermidis secretome, on the other hand, promotes the activity of regulatory T-cells (Treg), suppressing the proliferation of CD4-positive T cells. Furthermore, *S. epidermidis* induces the release of IL-10 by skin dendritic cells.³¹

It becomes obvious that changes in skin microbiome are most critical during early life time, when skin barrier function and immune system are rather immature. Skin microbiome is dynamic since it changes with time. Operational taxonomic unit (OTU) stability of skin microbiome has been found less abundant and therefore more instable than that of intestinal microbiome, probably due to cleaning and other extrinsic factors.^{32,33}

Intestinal microbiome and AD

The fetal intestine becomes colonized before delivery by bacterial transmission from the mother through the placental barrier. The mode of delivery has further impact on intestinal microbiome. It has been demonstrated that delivery by cesarean section decreases the colonization by *Bacteroides* but increases the number of *Clostridia*.³⁴

It has been assumed that small intestine permeability may be increased in AD patients.^{35,36} Intestinal permeability is one factor in acquired food allergy.³⁷

Disturbances in intestinal microbiome could be a risk factor of further AD development. Intrapartum antibiotic use for >24 h increased the relative risk for AD infants at the age of 2 years by 1.99.³⁸

Staphylococcus aureus was isolated from rectal swabs from infants aged 0 to 2 months. *S. aureus* strains of infants who developed AD were different from the strains of infants who were not affected at the age of 18 months. A combination of expression of superantigen SEIM and adhesin elastin-binding protein by *S. aureus* was protective for AD.³⁹

High fecal calprotectin at the age of 2 months is a risk factor for AD. There is an inverse correlation to intestinal *Escherichia coli* colonization. It can be concluded that early intestinal colonization by *E. coli* has long-term health implications and is a protective measure for AD.⁴⁰

A South Korean study investigated the intestinal microbiome in 90 AD and 42 non-AD subjects. They observed an enrichment of *Faecalibacterium prausnitzii* F6 in AD, most

distinct in the youngest patients, leading to a decreased intestinal concentration of butyrate and propionate.⁴¹

Another study used microarray analysis of intestinal microbiome in infants with and without AD at 6 and 18 months of age. Although the authors did not find significant differences at 6 months, healthy children at 18 months harbored threefold greater number of *Bacteroidetes*. Infants with AD showed increased numbers of *Clostridia*.⁴²

Intestinal microbiome is dynamic during the first 3 years of life before stabilizing.⁴³ In contrast to skin microbiome, intestinal microbiome demonstrates heritability as demonstrated by a recent metagenomics shotgun sequencing study in adult twins.⁴⁴

Microbiome in the treatment of AD Therapies targeting skin microbiome

There is much evidence suggesting a link between impairment of epidermal barrier function and disturbed skin microbiome.^{15,22}

Antibiotics and antiseptics may decrease skin colonization by *S. aureus* but fail to improve the microbiome. On the other hand, topical treatments with corticosteroids, calcineurin inhibitors or even moisturizers and emollients are capable to restore barrier function and normalize skin microbiome.^{22,45,46}

To restore cutaneous microbiome in AD, transplantation of microbiota from healthy volunteers might become an option. Skin culturable Gram-negative microbiome differs between AD patients and healthy controls. In a mouse model of AD, culturable Gram-negative bacteria such as *Roseomonas mucosa* from healthy volunteers reduced the growth of *S. aureus*, enhanced skin barrier function and activated innate immune function.⁴⁷ In the future, such a treatment may become available for human patients.

Textiles serve as our second skin. Functional textiles may improve skin quality. Chitosan-coated long-sleeve pyjama tops and pants worn overnight for 8 weeks improved the severity scoring of atopic dermatitis index from baseline in 43.8% of patients whereas only 16.5% improved with the uncoated pyjamas. A significant decrease in coagulase-negative *Staphylococci* was observed on the skin with the chitosan-coated product.⁴⁸

Another open trial investigated the effect of ZnO fabrics on AD severity in adult patients. The fabric was used overnight on three consecutive days. ZnO has antibacterial activity and serves as an oxygen radical scavenger. Severity of AD, pruritus and sleep quality of patients improved even after short-time application of the functional textile.⁴⁹

A meta-analysis evaluated published studies about functional textiles in AD. Fabrics based on silk, silver-coated cotton, borage oil and ethylene vinyl alcohol (EVOH) fibers

were analyzed. Silk and silver-coated cotton demonstrated the strongest effects on AD severity, but only silver-coated cotton reduced *S. aureus* colonization of skin.⁵⁰

On the other hand, it is questionable whether this attempt would have any impact on dermal and subcutaneous adipose tissues, which are a substantial part of cutaneous microbiome.¹⁶

Therapies targeting intestinal microbiome

Probiotics are defined as live microbial food ingredients that confer health benefits for the consumer.⁵¹ In most AD studies, probiotics have not shown a beneficial effect, independent of the age of AD patients.⁵² Two recent meta-analyses, however, found best evidence for probiotic supplementation in mothers and infants for *Lactobacillus rhamnosus* GG in long-term prevention of AD.^{53,54}

In a prospective randomized trial, the oral application of *Lactobacillus salivarius* LS01 and *Bifidobacterium breve* BR03 for 12 weeks to adult patients with AD improved severity (as measured by the SCORAD index), quality of life (dermatology quality of life index) and ratio of Th17 to Treg cells and diminished immune activation and microbial translocation.⁵⁵

In a mouse model, AD was improved by oral administration of *Lactobacillus casei var. rhamnosus* (LCR35), which increased the gut population of *Bacteroides fragilis*, *Lactobacilli*, *Bifidobacterium* and *Enterococcus*, while *Clostridium coccooides* became less frequent. The treatment also restored the Th1/Th2 balance.⁵⁶

Oral administration of the probiotic *Bifidobacterium animalis subsp lactis* (LKM512) alleviated pruritus in adult AD patients in a placebo-controlled prospective trial. Metabolomic analysis suggested that the antipruritic effect was due to increased production of fecal kynurenic acid.⁵⁷

In an open trial, 130 pregnant women were treated with *B. breve* M16V and *Bifidobacterium longum* BB536 1 month before delivery; 36 mother–infant pairs served as controls. After delivery, the infants were treated for 6 months with the same combination of probiotics. The risk of AD was significantly reduced within the first 18 months of life (odds ratio at 18 months: 0.304). Temporary changes in intestinal microbiome were noted in infants who developed AD.⁵⁸

A meta-analysis of randomized controlled trials suggested the highest efficacy in reduction of severity of AD and prevention of AD by synbiotics, i.e., a combination of prebiotics and probiotics with a mixture of different microbial strains, in children >1 year of age.⁵⁹

Primary prevention of AD in infants by probiotic supplementation of their breast-feeding mothers 2–4 weeks before delivery failed in a randomized, double-blind trial.⁶⁰

Prebiotics are defined as selectively fermented nutrients that cause specific changes in composition and/or activity of intestinal microbiome.⁶¹ The first randomized controlled trial in infants at high risk for AD included 259 patients during their first 6 months of life. The verum group got a mixture of prebiotic galacto-oligosaccharides and long-chain fructo-oligosaccharides. At the end of this trial, 9.8% in the verum group and 23.1% in the placebo group developed AD, demonstrating a preventive effect of prebiotics. On the other hand, severity of AD was not affected by prebiotics.⁶²

Two prospective randomized and placebo-controlled trials in infants using either prebiotic galacto-oligosaccharides or a mixture of prebiotics failed to reduce severity of AD.^{63,64} Another trial in low-risk infants suggested a temporary preventive effect on AD.⁶⁵

Most of these trials observed changes in intestinal microbiome with increased numbers of *Bifidobacteria* but reduced numbers of *Clostridiae*.^{63–65}

Daily intake of *Lactobacillus plantarum* YIT 0132-fermented citrus juice (LP0132-fermented juice) alleviated AD symptoms in adults during 8 weeks of treatment and further 8 weeks off treatment in two open trials.⁶⁶

Fecal microbiome transplantation has been successful in some intestinal diseases such as recurrent *Clostridium difficile*-induced pseudomembranous enterocolitis and Crohn's disease, but data on AD are still missing.^{47,67}

Conclusion

AD is a common inflammatory skin disease. Recent investigations suggested a role of skin and intestinal microbiome in AD. Most data have been observed from infants, and those from other age groups are rather limited. Furthermore, data from populations less often affected by AD than Caucasians and Asians are almost nonexistent.

Skin microbiome includes not only superficial stratum corneum that is affected by environmental factors such as exposure to germs and cleansing. Available evidence argues for a link between epidermal barrier impairment and disturbances in skin microbiome in AD.

Until today, studies considering the different compartments/tissue layers populated by skin microbiome in AD have not been investigated in detail.

In contrast to skin microbiome, intestinal microbiome seems to become stabilized after infancy. There is also a significant heritable component for intestinal microbiome. The microbial taxa, relative percentages and quantities vary remarkably between the different parts of the intestinal tract.

Skin barrier-aimed topical treatments help to develop a neo-microbiome from deeper compartments. Probiotics, prebiotics and synbiotics have been investigated for the treatment of AD, but further investigations are needed. Current understanding suggests that there may be a window of time to gain best results before the age of 3 years. Normal delivery and avoidance of antibiotics in the perinatal period seem to have a preventive effect in AD. Targeted treatment options to normalize skin and intestinal microbiome in AD are under investigation.

Disclosure

The author reports no conflicts of interest in this work.

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