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Host-microbiome interactions in the holobiome of Atopic Dermatitis

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19 Introduction

20 Atopic dermatitis (AD) is a multifactorial disease that is now understood to involve underlying
21 genetic abnormalities in the immune and epidermal barrier of the skin, environmental drivers, and
22 dysfunction within the microbial community. Increased knowledge of the composition of the skin
23 microbiome in AD, demonstrated first by a series of descriptive reports and more recently by uncovering
24 the relevant mechanisms for communication between the microbiome and the host, has been critical to
25 recent progress in therapy. Today however, we are poised to gain further insight into the pathogenesis of
26 AD by integrating into one system the knowledge gained through separate studies of classical immunity,
27 the epidermal barrier, and microbes. This can be done by applying holobiome theory to AD; a fundamental
28 biological concept that has been discussed for decades in a variety of non-human ecologies (1). This theory
29 recognizes the intimate connection between the host and its microbial accomplices and has led to
30 understanding how companion, mutualistic microbes are essential for survival of many organisms in
31 nature such as plants and invertebrates. Recognizing that the host-microbiome combination is essential
32 for immune defense of human skin enables a better understanding of how our microbial associates help
33 to maintain health but can also contribute to disease in AD. Indeed, no disease better reflects the
34 importance of the holobiome to human health than AD (**Figure 1**).

35 The cutaneous microbiome as both friend and foe in atopic dermatitis

36 The microbiome is established early in life and evolves as an individual transition from childhood
37 to adulthood. The maternal and environmental milieu shape a newborn's microbiome, which is now
38 understood to have long-lasting implications, but the specific factors that predict this are nuanced,
39 precede delivery, and extend throughout life (2). Much is still left to be uncovered on this subject, but
40 current evidence suggests that early infant bacterial exposures have long term impacts: colonization with
41 commensals correlates with lower risk of developing AD, while early *S aureus* exposure increases risk of
42 developing AD in the future (2). The microbes that survive on the skin and other barrier surfaces are not
43 explained only by hygiene, a hypothesis that has been largely debunked (3). We now appreciate that key
44 connections established between the cutaneous microbiome can drive disease or protect us from it.

45 Detrimental organisms that promote disease in AD include *Staphylococcus aureus*, where higher
46 bacterial burden correlates with increased AD severity (2). *S. aureus* colonization precedes development
47 of AD lesions, and colonization drives skin inflammation through multiple pathways. Specific *S. aureus*
48 gene products that contribute to AD (including proteases, phenol-soluble modulins (PSMs), toxins, TLR
49 ligands, superantigens, adhesions) disrupt host epidermal barrier and impact innate and adaptive immune
50 responses. However, it is important to remember that not all patients with AD are colonized with *S.*
51 *aureus*, indicating that many additional drivers contribute to AD pathogenesis. Other members of the
52 commensal skin microbial community can contribute to disease in the absence of *S. aureus*. These include
53 *Staphylococcus epidermidis*, typically an important commensal that is a pathobiont. *S. epidermidis* can
54 benefit the skin by promoting expression of antimicrobial peptides along with decreasing inflammation,
55 but like *S. aureus* can overgrow on AD skin and act damage the host in part by production of the protease
56 EcpA (4, 5).

57 While many of the gene products of microbes affect the host, the host in turn regulates the
58 composition of the skin microbiome by several mechanisms. Early insight into host defects in AD came
59 with recognition that mutations in genes within the epidermal differentiation complex such as filaggrin
60 can contribute to development of disease and contribute to the physical defense barrier of the epidermis.
61 Also, the skin of AD patients has inadequate production of host antimicrobial peptides (including
62 cathelicidins and β -defensins) due to excess Th2 signaling (6). Additionally, numerous environmental
63 factors (including antibiotic exposures, pollution, bathing practices, and maternal microbiome) can play
64 exacerbating roles in AD. However, this perspective of host-centric defense mechanisms is providing an
65 incomplete picture of the factors that control the function of the holobiont. Another important skin

defense system comes from other commensal bacteria, including *S. epidermidis*, that in addition to the beneficial functions described earlier, can produce antimicrobial bacteriocins to regulate the expansion of *S. aureus* on the skin (5). These beneficial functions are not universally produced by all members of this species but rather occur only in specific strains. Loss of these specific beneficial strains, combined with the inadequate production of the host antimicrobial peptides from the host, sets up a double-hit leading to further overgrowth of damaging microbes that promote inflammation. Furthermore, as many of the bacterial genes that cause damage to the skin are under control of a quorum sensing system, another protective action from some members of the skin microbiome comes from the capacity to secrete peptides that block quorum sensing, thus limiting the *S. aureus* and *S. epidermidis* toxin production and controlling damage to the epidermis (7). Overall, the field continues expanding our understanding of bacterial drivers and bacterial preventors of AD.

Evidence from therapeutic interventions

As more therapeutic interventions are explored to treat AD, we gain further understanding of disease pathophysiology. The improvement in AD severity that occurs with blockade of IL4-R α by the monoclonal antibody dupilumab also increases overall microbial diversity and decreases *S. aureus* abundance, and this decrease in *S. aureus* precedes the improvement in disease (8). Decreased total bacterial abundance and improvement in eczema severity scoring was still observed months after treatment terminated, suggesting long-term impacts. More recent analyses show lower rates of severe infections in dupilumab-treated patients in both adults and children, suggesting that this microbiome shift is protective against pathogenic species (9). Multiple new therapeutics for use in AD patients (including targeting IL13, the Janus Tyrosine Kinase (JAK) inhibitors and Aryl hydrocarbon receptors (AhR) will likely also influence bacteria residing on the skin, but their impact on the microbiome is still unknown.

The potential power of applying holobiome theory can be illustrated by recent interventional studies harnessing commensals to decrease *S. aureus* and improve AD. These have substantial theoretical benefit by enhancing host defense without weakening the host immune system. For example, controlled clinical trials using specific strains of commensal Staphylococcal species as a topical therapy to AD lesions improved eczema severity (10). Mechanistically, both human and animal trials found this intervention resulted in decreased levels of *S. aureus*, inhibition of quorum sensing and decreased expression of the inflammation-inducing toxin, *psma* (10). However, not all therapeutic attempts with topical live bacteria have been successful. Early promise with *Roseomonas mucosa*, a soil bacterium sometimes found on human skin, failed to show dramatic benefit in AD in controlled trials (2). Bacteriotherapy approaches to disease offer a unique benefit of not being immunosuppressive and not using broad spectrum antibiotics that promote drug resistance. However, thus far, bacteriotherapy trials in the skin have been limited by small study size and short duration, and the question remains if the patients' AD severity and microbial composition will ultimately return to pre-trial baseline, or if the transplanted commensals will establish residence in the skin follicle and provide protection against inflammation and *S. aureus* colonization over the long-term.

Future directions

In the past, research in AD has focused heavily on increasing understanding of the immune system alone. Today, we see that a delicate balance exists between the skin barrier, immune cells, commensal microbes and potential pathogens (including interspecies crosstalk, quorum sensing, and the ability of bacteria to regulate host AMP production and immune response). Microbiome research in AD has largely centered around the role of *S. aureus* and other staphylococcal species. Newer technological advances are opening the doors for exploration of the fungi and viruses in the microbiome, which will offer a more comprehensive understanding of holobiome function in the development of AD. Many questions remain on why some patients' microbiomes are more susceptible to the cascade of bacterial population shift towards dysbiosis and increased inflammation, while others remain in homeostasis. Newer studies taking

a more personalized approach to AD by addressing everyone's skin defense system along with their microbiome may prove to have the most long-term impact. As interventional therapies targeting the skin microbiome with the goal of decreasing severity or completely averting development of AD continue, we will expand our long-term understanding of this balance and find novel treatments to impact this disease. A comprehensive approach to the skin holobiome in AD offers the best hope to provide successful long-term prevention, treatment or cure.

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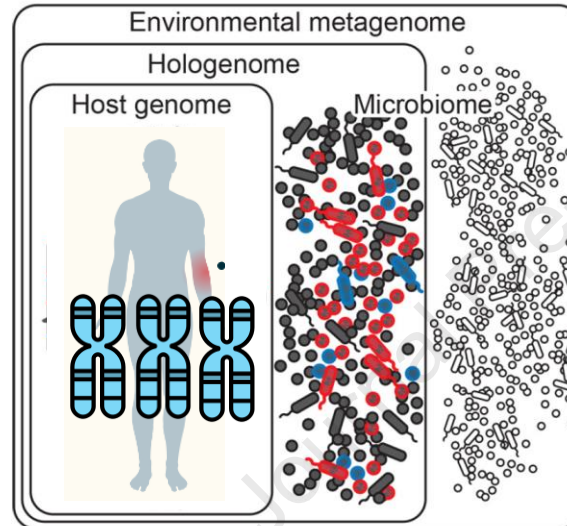
Figure legend

Figure 1: The Atopic Holobiont. The combination of human and microbial gene products that influences health of the organism is called the hologenome. The functional unit of the atopic holobiont results from the combined functions of human genetic factors (such as alterations in filaggrin, innate and adaptive immunity defects), environmental exposures, and microbial gene products. Specific strains from multiple categories of microbes directly interact with the human host. These strains can act as pathogens and pathobionts (such as *S. aureus*, *S. epidermidis*, *C. acnes*, *M. furfur*), beneficial, mutualistic microbes (including *S. hominis* and *S. epidermidis*), and commensal microbes (which do not induce host changes). Pathobionts are microbial strains that are not always damaging and these organisms as well as true pathogens drive host barrier damage and inflammation through a number of proteases, toxins, adhesins, superantigens. Mutualistic microbes act synergistically with the host to protect the barrier by expressing factors including antimicrobials (lantibiotics, bacterocins) and autoinducing peptides that regulate toxin production from pathogens. Environmental microbes (such as water and soil microorganisms) do not influence the health of the holobiont at baseline, although some act as opportunistic pathogens, especially when there is significant barrier dysfunction or immunosuppression.

The Atopic Holobiont

Human

FLG
CARD11
KIF3A
IL4Ra
Th2 cytokines
Antimicrobial peptides
Lipids
Allergen exposure
Host behaviors



Microbes

Pathogens and Pathobionts

i.e. S. aureus, S. epidermidis,
C. acnes, M. furfur

Proteases, toxins, adhesins,
superantigens, etc.

Mutualistic microbes

e.g. S. hominis, S. epidermidis

Lantibiotics, bacterocins,
Autoinducing peptides, etc.

Commensal Microbes

Have no action on the host

Environmental microbes

Not part of holobiont