THROUGH A MICROSCOPIC LENS: SKIN MICROBIOME AS THE CONFEDERATE IN ATOPIC DERMATITIS

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ABSTRACT

Reciprocity between the skin microbiome and the host underlies the occurrence, exacerbation, and severity of atopic dermatitis (AD). However, the role of the skin microbiome in the pathogenesis of AD is yet to be depicted. This review highlights thehost–microbiome interactions which rely on barrier status, microbiome composition, andmicrobe–microbe interactions. A microbiome shift, with an abundance of S. aureus and lower microbial diversity, compromises the skin barrier function.

It shows that epidermal barrier defect depletes the protective commensal skin bacteria and demonstrates how dysbiosis of the skin microbiome can lead to AD.

Keyword: *atopic dermatitis, skin microbiome, dysbiosis.*

ABSTRAK:

Interaksi antara mikrobiota kulit dan kulit pejamu memiliki peran di balik manifestasi, tingkat keparahan, dan eksaserbasi dermatitis atopik (DA). Akan tetapi, peranan mikrobiota kulit dalam patogenesis DA masih belum sepenuhnya dijabarkan. Ulasan ini berfokus pada interaksi kulit pejamu-mikroba kulit yang bergantung pada keadaan sawarkulit, keanekaragaman mikrobita, serta interaksi antar mikroba-mikroba kulit. Perubahan komposisi mikrobiota, dengan adanya peningkatan *S. aureus* dan penurunan keragaman mikrobiota menurunkan fungsi sawar kulit. Hal ini membuktikan bahwa mikrobiota komensal yang ditemukan pada kulit berperan penting dalam melindungi kulit terhadap patogen, serta menunjukkan bagaimana disbiosis mikrobita tersebut dapat menyebabkan DA.

Kata kunci: dermatitis atopi, mikrobiota kulit, dysbiosis

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INTRODUCTION

The atopic dermatitis (DA) is a prevalent chronic skin disease, affecting about 20% of children and 5% of adults.[1,2] A substantial number of patients suffer from severe or persistent AD and experience a devastating impact on their well-being.[3] Furthermore, persons with AD renders an onerous financial implications.[4]

The epidermis functions as a functional and physical interface between the body and the environment. Epidermal disruption is a central pathologic process in AD.[5] With such compromise, AD skin is associated with marked changes in the composition of the skin microbiome (dysbiosis), forming part of a complex interplay with skin barrier integrity and giving rise to the waxing and waning course AD.[6] This review illustrates how abnormalities of the epidermal barrier in AD generate dysbiosis, which results in increased inflammatory cytokines and disease exacerbation.

SKIN MICROBIOME DEFINITION

Skin microbiota is an interrelated ecosystem comprising not only bacteria but also symbiotic fungi and viruses. The equibilirium and wholeness of these microbial diversity plays a pivotal role in preventing pathogens from pervading the skin.[7,8]

Healthy human skin commonly harbors several bacteria genera, including: *Staphylococcus*, *Corynebacterium* and *Cutibacterium*. Each genera has its topographical assortment.[9] For example, *Staphylococcus* and *Corynebacterium* species more commonly reside in moist areas, while *Propionibacterium* species (recently renamed *Cutibacterium*) generally inhabited sebaceous areas. The *Malassezia* fungus is mostly found on the truncal area and upper extremities.[10]

Although the majority of these microbiome are harmless and even advantageous, some are potentially pathogenic under certain conditions and are referred to as “pathobionts”. Marked changes (dysbiosis) in the configuration of the skin bacterial microbiome, as found in AD, afflicts the skin barrier integrity.[11]

SKIN MICROBIOME DISRUPTION IN AD

The species *S. aureus* colonizes AD skin and is only found in a small proportion of healthy control skin.[12,13] In AD skin, there is a difference in microbiome composition between lesional and nonlesional skin. For example, there is a lower bacterial diversity in AD flexures, with an abundance of *S. aureus* and *S.*

epidermidis species.[14,15] The abundance of *staphylococcus* progressively increase from non-lesional skin samples over acute to chronic lesions; with a significantly higher abundance of *staphylococci* in chronic lesions compared to nonaffected skin.[16]

This dysbiosis is positively correlated with AD flares, proven by a temporal relationship linking microbiome shift and AD exacerbations; and recovery of microbial diversity following treatment.[17,18]

Not only does colonization of *S. aureus* leads to AD flares, but it is also associated with more severe exacerbation of AD.[19,20] As a matter of fact, the clinical link between *S. aureus* burden and AD severity has been proven through cultural studies; with an inverse correlation between the abundance of the protective commensals, *S. epidermidis and Corynebacterium,* relative to *S. aureus*.[15,21–23] These commensals can induce antimicrobial peptides (AMP) which inhibit *S. aureus* colonization on human skin. Thus, the depletion of these commensal species consequently depletes the likely regulatory or protective commensals.[15,24,25]

Methicillin-resistant Staphylococcus aureus (MRSA) colonization in AD is associated with a more profound change in the composition of commensal bacteria[26] and gives rise to an oppressive inflammatory reaction, as opposed to skin that is populated by Methicillin-resistant Staphylococcus aureus (MSSA) establishment.[27,28]

A systematic review showed that there is also a reduced number of *Malassezia* species and greater diversity of other fungal genera (excluding *Malassezia, Aspergillus, Candida,* and *Cryptococcus* genera).[22]

ROLE OF EACH MICROBIOTA IN AD

One way the host responds to abundantly colonized *S. aureus* in AD lesion is via antimicrobial defense mechanism. This may be done by commensal bacteria, such as *S. epidermidis* through the production of AMP, and by *C. acnes* through lipid utilization.[29]

A recent study confirmed that *S. Epidermidis* can specifically limit *S. aureus* growth[30] and suppress inflammation via activation of APC and secretion of anti-inflammatory IL-10.[31] In addition, *S. epidermidis* also secretes a lipoteic acid which suppresses both keratinocytes inflammatory cytokines and inflammation through a TLR2-dependent mechanism.[31]

A study was done by Nakatsuji found that *Coagulase-negative Staphylococcus* (CoNS), a commensal bacteria, protects normal skin from *S.*

aureus colonization. Conversely, deficiency in commensal bacteria is associated with establishing *S. aureus* in AD skin.[25] The growth of *C. acnes*, which particularly depends on the presence of fatty substrate in the skin, might be restricted in AD.[16] One study demonstrated that a higher quantity of *C. acnes* is inversely correlated to the number of *S. aureus* colonization.[32] It has been confirmed that *C. acnes* is capable of producing propionic acid, a short-chain fatty acid (SCFA), through the fermentation glycerol which restricts *S. aureus* growth.[33]

It is still controversial whether *Malassezia* plays a role in AD. Perhaps it is associated with its pathogenicity, as seen in AD patients with more prominent symptoms on the head and neck. Nevertheless, studies identified a decrease in *Malassezia* in AD.[34,35] One of the studies was done in a group with previous AD exacerbation, not on antifungus medication.[34] In short, dry AD skin and deprivation of *C. acnes* which produces substances essential for *Malassezia* growth, creates a poor growing condition for *Malassezia.*[34,3]

PATHOGENESIS

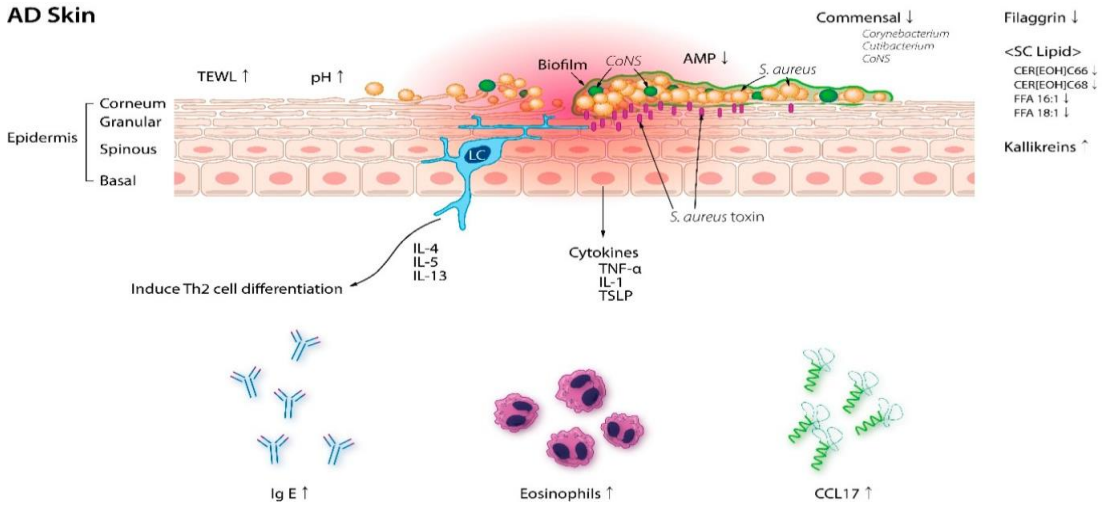

Figure 1: Pathogenesis of dysbiosis and AD [36]

There are three critical factors in the pathogenesis of AD: epidermal barrier dysfunction, changes in the microbiome composition, and abnormalities of the skin immunity related to T-helper 2 (Th-2). These factors may reciprocate and retaliate against each other.[37]

Impaired Skin Barrier

The interplay between multiple risk factors increases the risk of skin barrier impairment, thus favoring *S. aureus* colonization on AD skin. These factors include the reduction of filaggrin and filaggrin degradation products (FDPs), altered lipid profiles, the strength of *S. aureus*-corneocyte adhesion, microbial dysbiosis resulting in the deficiency of AMPs, and overexpressed Th2 cytokines.[38,39]

Pyrrolidone carboxylic acid and urocanic acid are examples of filaggrin and FDP. Both have the ability to maintain skin pH and inhibit the growth of *S. aureus* on the skin [40]. The lack of filaggrin in AD results in a higher pH, a condition approbative for *S. aureus* growth, therefore inducing more skin barrier impairment.[24,41,42]

In AD skin, reduced filaggrin and FDP increases the adherence of *S. aureus* to epidermal cells.[43,44] Other factors that favors *S. aureus* adhesion (to bronectin, loricrin and cytokeratin 10) are deformed corneocyte and presence of clumping factor B and fibronectin- binding proteins.[43]

The fatty substrate of the skin; such as free fatty acid, ceramides, and sphingosine; essentially maintains the integrity of the skin barrier and prevents pathologic colonization of *S. aureus*.[45] An in vitro study proposes that exogenous FFA 16:1 also has a potent bacterial inhibiting features.[46] Unfortunately, this lipid metabolism and composition is altered by the highly conveyed Th2 in AD.[38]

At a physiologic state, the skin's pH is preserved at a level of < 5,5. This protective acidity is maintained by anaerobic bacteria, such as *Finegoledia spp.* and *Lactobacillus spp.*, through the fermentation of FDP which generates short chain fatty acids, lactic acid, and propionic acid. Not only do they conserve a favorable pH for the skin ecosystem, but these substances also have a role in the activation of AMP at the time of skin injury. However, this protective role may be ablated in AD, as there is enhanced oxygenation, thus decreasing the quantity of these anaerobic bacteria. This (menjelaskan kalimat yang mana?) creates a good environment for *S. aureus* colonization.[47]

Dysbiosis

The leaky epidermal skin barrier in AD permits the entry of environmental and cutaneous pathogens and immunogens, causing skin dysbiosis.[48] Skin dysbiosis, and vice versa, disrupts the epidermal barrier, either directly or indirectly.[49,50] Altogether, this propels an endless loop of

inflammation, itch, and more skin barrier breakdown.[48]

Decreased number of commensals, thus decreased expression of AMP, including cathelicidins and β-defensins, causes skin dysbiosis and skin barrier defects.[23,24] It also creates an advantageous environment for *S. aureus* colonization.[51] Despite that, higher expression of interleukin (IL)-4 and IL-13 in AD down-regulates LL-37 and HBD-3.[51,52]

S. aureus colonization is strongly associated with an even worse barrier dysfunction. Perhaps, this is due to the assembly of biofilm, which can induce more profound skin inflammation.[36] A biofilm is a bacterial product that is enclosed in an extracellular matrix and adheres to the corneocyte. This biofilm formation produces immune deterrence, precipitating AD recurrences and causing difficult-to-treat infection.[53]

The colonizing *S. aureus* then generates offending factors, notably: enzyme, toxin, and protein, that promotes skin barrier dysfunction and inflammation in AD. These include: phenol-soluble modulins δ-toxin, superantigens, protein A, proinflammatory lipoproteins, and proteases.[43]

Serine proteases from *S. aureus* are also involved in barrier disruption and type 2 inflammation.[54] Additionally, α-toxin, a fundamental *S. aureus* toxin, induces the death of skin cells and further epidermal defect.[55]

T-Helper 2 Immunity

Colonization of *S. aureus* in AD results in a more intense hapten sensitization, more pronounced Th-2 expansion, and dire skin impairment.[23,43]

The greater inflammatory reaction has recently been recognized to correspond to *S. aureus* colonization. This is mainly due to the initiation and expansion of Th-2 cytokine shift prompted by *S. aureus* Other mechanisms involved in this grueling inflammatory response include: deliberation of chemokines and proinflammatory substrates, production of IL (for instance IL-31) following degranulation of mast cell, as well as augmentation of B cell (independent of T cell).[43,56]

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