Perspective

Skin Microbiome: An Actor in the Pathogenesis of Psoriasis

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INTRODUCTION

Psoriasis is characterized by raised, scaly, well-demarcated, erythematous oval plaques.[1] Although studies have revealed that disruption of immune tolerance and excessive production of inflammatory factors play important roles in the pathogenesis of psoriasis, the exact mechanism is still not clear.[2] Previous studies have shown that the concordance rate of monozygotic twins with psoriasis is greater than that of dizygotic twins,[3,4] with genetic factors underpinning 66–90% of the variation in risk of developing psoriasis.[5] These studies reveal not only the genetic influence on psoriasis but also that nongenetic factors are important in the pathogenesis of psoriasis.

Each one of us is colonized by some 100 trillion bacteria that reside in our intestines, mouth, nose, genitals, and skin.[6] As a critical barrier to the outside world, human skin is the body’s largest and most exposed organ. Human skin closely interacts with the exterior environment, and the commensal microbiota at the skin play an important role in maintaining the function of skin barrier.[6] An assemblage of microorganisms, including bacteria, fungi, viruses, and arthropods, colonize the human skin and together form the skin microbiome.[7] The skin microbiome plays an important role in maintaining human health through inhibition of invasion by pathogens, formation of biofilms, and production of antibacterial peptides. Recent studies indicate that the composition of the human skin microbiome is closely related to many diseases including atopic dermatitis,[8] psoriasis,[9] and acne vulgaris.[10] In this review, we will focus on the relationship between the skin microbiome and the function of the skin barrier, the microbiome changes in psoriasis, and the possible pathogenic mechanisms involved.

SKIN MICROBIOME AND THE SKIN BARRIER

Because skin is protective against physical, biological, and chemical stress, it is considered to be an effective barrier between the body and the environment.[11] The skin consists of epidermis, dermis, and hypodermis. Epidermis is stratified into four layers according to the stage of keratinocyte differentiation: stratum corneum, stratum granulosum, stratum spinosum, and stratum basale.[11] The skin barrier is formed by differentiating keratinocytes and is continuously renewed. Previous studies have showed that the stratum corneum and epidermal tight junctions are two of the main elements in the barrier function of the skin.[13] The microbial ecology of human skin is complex and may play an important role in diseases. Studies focusing on healthy volunteers have demonstrated that Staphylococcus, Micrococcus, Corynebacterium, Brevibacteria, Propionibacteria, and Acinetobacter species regularly reside in normal skin.[14] The most common fungal species present on normal human skin are Malassezia.[15] A study of 11 body locations (the forehead, left and right axillae, left and right inner elbows, left and right forearms, left and right forelegs, and behind the left and right ears) from eight healthy adult participants showed that Malassezia accounts for up to 80% of the fungi on the skin.[16] Both environmental and host factors can affect the skin microbiome such as climate, body location, age, and gender.[17] For site-specific composition, the skin microbiome...
was found to be quite different across the population. However, when skin sites with bilateral symmetry were compared, the intraindividual variability of the skin microbiota had a high level of conservation.\textsuperscript{14,18}

\textit{Staphylococcus} has been associated with impaired wound healing in both clinical and laboratory models. Mullikin \textit{et al.} found that a longitudinal selective shift of microbiota coincided with aberrant expression of innate immunity genes in diabetic mice. Moreover, they detected aberrant expression of innate immunity genes associated with the significantly enriched cutaneous host defense response and increased \textit{Staphylococcus} abundance.\textsuperscript{19} Zeeuwen \textit{et al.} showed that \textit{Propionibacterium} was the dominant genus in the early recolonization phase during healing of superficial wounds.\textsuperscript{20}

### Skin Microbiome and Skin Inflammation

Previous studies have showed that skin microbiota is involved in the balance of cutaneous inflammation and anti-inflammatory processes. Germ-free (GF) mice have reduced interferon-\(\gamma\) produced by \(\alpha\beta\) T-cells and reduced interleukin (IL)-17A produced by \(\gamma\delta\) T-cells but have an increase in Foxp3\(^{+}\) Treg cells in the skin compared with specific pathogen-free (SPF) mice. In addition, application of \textit{Staphylococcus} to the epidermis of GF mice can restore the production of IL-17A by T-cell receptor \(\beta^{+}\) (TCR\(\beta^{+}\)) T cells in the skin. MyD88 and IL-1R1 knockout mice have reduced IL-17A production from TCR\(\beta^{+}\) cells in the skin.\textsuperscript{21,22} Together, these data suggest that skin commensals are important in the inflammatory T-cell response.

Filaggrin plays a crucial role in maintenance of the skin barrier. In lesioned skin from filaggrin-deficient flaky tail (Flg\(^{ft/ft}\)) mice raised in SPF conditions, dermal eosinophils, neutrophils, and expression of IL-17A mRNA were significantly increased in comparison with GF Flg\(^{ft/ft}\) mice.\textsuperscript{23,24} Lai \textit{et al.} found that \textit{Staphylococcus epidermidis} can suppress inflammatory cytokine release from keratinocytes through a TLR3-dependent mechanism.\textsuperscript{25}

### Skin Microbiome and Skin Immunity

Both the innate and adaptive immune systems play roles in the immune function of skin.\textsuperscript{26} The innate immune system is considered as a sentinel for detecting invasion by microorganisms. By releasing antimicrobial peptides, chemotactic proteins, and cytokines, keratinocytes, Langerhans cells, mast cells, dendritic cells, and macrophages provide an early warning system.\textsuperscript{27,28} Using T- and B-cells expressing antigen-specific receptors, the adaptive immune system provides more broad and flexible response to pathogens. It is regarded as a means for providing memory of previous pathogen encounters. At the skin interface, this process involves three stages: increasing the efficiency of naive T-cells that are exposed to antigens, targeting the effector response to the most appropriate tissue site, and expanding coverage to other tissues.\textsuperscript{29}

It has been proposed that the skin microbiome greatly impacts upon human immune functions. However, the mechanisms associated with this role have remained elusive. The mechanisms probably include inhibiting the growth of pathogenic microbes, enhancing host innate immunity, and educating adaptive immunity.\textsuperscript{30} \textit{S. epidermidis} is a common commensal bacterium of the skin, whereas \textit{Staphylococcus aureus} is a human pathogen. A study conducted by Iwase \textit{et al.} showed that \textit{S. epidermidis} can inhibit \textit{S. aureus} biofilm formation.\textsuperscript{30} In another study, after inoculation of the upper arm, swabs were taken at multiple time points for \textit{Haemophilus ducreyi}. Papules either spontaneously resolved or progressed to pustules, with the microbiomes differing between the two groups. \textit{Proteobacteria}, \textit{Bacteroidetes}, \textit{Micrococcus}, \textit{Corynebacterium}, \textit{Paracoccus}, and \textit{Staphylococcus} species were more abundant at pustule-forming sites, whereas resolved sites had a greater abundance of \textit{Actinobacteria} and \textit{Propionibacterium} species.\textsuperscript{31} Shu \textit{et al.} demonstrated that \textit{Propionibacterium acnes} can inhibit the growth of methicillin-resistant \textit{S. aureus}.\textsuperscript{32} Together, these findings illustrate a crucial role for commensal bacteria in the host immune defense against pathogens.

### Skin Microbiome and Skin Psoriasis

Psoriasis is a chronic inflammatory skin disease and a genetically disposed immune disorder. Psoriasis can be provoked or exacerbated by specific pathogens including bacteria (\textit{S. aureus} and \textit{Streptococcus pyogenes}), viruses (human papillomavirus and endogenous retroviruses), and fungi (\textit{Malassezia} and \textit{Candida albicans}).\textsuperscript{33} Alekseyenko \textit{et al.} showed that the abundances of \textit{Corynebacterium}, \textit{Propionibacterium}, \textit{Staphylococcus}, and \textit{Streptococcus} were significantly increased in psoriatic plaques.\textsuperscript{30} Fahlin \textit{et al.} found that streptococci were the most common genera in both normal and psoriasis skin, whereas staphylococci and Propionibacteria were significantly lower in psoriasis compared with control limb skin.\textsuperscript{35} Consistent with the former, Gao \textit{et al.} revealed that \textit{Propionibacterium} species were less abundant in psoriasis than in normal controls.\textsuperscript{39} In another study, a reduction in \textit{Firmicutes} and an increase in \textit{Proteobacteria} were found in psoriatic patients.\textsuperscript{36} Liew \textit{et al.} found that \textit{Firmicutes} were significantly overrepresented in psoriatic lesions in comparison with uninvolved skin in patients and in healthy controls. \textit{Actinobacteria} and \textit{Propionibacterium} were significantly underrepresented in the psoriatic lesion samples.

Using pyrosequencing of fungal rRNA from 12 psoriatic patients and 12 healthy controls, Takemoto \textit{et al.} showed that \textit{Malassezia} was the most abundant fungus in both groups. However, the level of \textit{Malassezia} colonization in psoriasis patients was lower than that in healthy controls. In general, the fungal microbiome of the psoriasis group was more diverse in comparison with the healthy controls.\textsuperscript{37} Supporting the former study, Paulino \textit{et al.}\textsuperscript{38} found that \textit{Malassezia restricta} was the most abundant species in six
healthy and two psoriatic skin samples; however, they found no significant difference in the microbiota of the two skin types. Horton et al. found that infections are associated with the development of pediatric psoriasis, but antibiotics use does not contribute substantially to that risk. Reduced bacterial biodiversity was noted in psoriatic patients. Xanthomonadaceae, which belongs to the Proteobacteria phylum, were associated with clinical improvement of psoriasis after a 3-week balneotherapy treatment.

Although further studies are required to establish an association between the cutaneous microbiome and psoriasis, current research suggests that the microbiome in patients with psoriasis is distinct from that of healthy controls.

In conclusions, the skin microbiome is closely associated with the functions of the skin barrier and immune system. Advances in sequencing technology have allowed us to characterize the skin microbiome and how it is altered in psoriasis. Future studies investigating the crosstalk between the human skin microbiome and the immune system, and their influences on psoriasis, will enhance our understanding of the occurrence, development, and relapse of psoriasis. Because skin is relatively accessible, further research and an improved understanding of the skin microbiome should lead to diagnostic and therapeutic applications.

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Conflicts of interest
There are no conflicts of interest.

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