Perspective

Skin Microbiome: An Actor in the Pathogenesis of Psoriasis

Wen-Ming Wang, Hong-Zhong Jin

Department of Dermatology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100730, China

Key words: Inflammatory Diseases; Psoriasis; Skin Microbiome

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.

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.4103/0366-6999.221269

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.[12] 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

Address for correspondence: Dr. Hong-Zhong Jin, Department of Dermatology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100730, China
E-Mail: jinhongzhong@263.net

Received: 17-08-2017 **Edited by:** Li-Min Chen
How to cite this article: Wang WM, Jin HZ. Skin Microbiome: An Actor in the Pathogenesis of Psoriasis. Chin Med J 2018;131:95-8.

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.[14,18]

Staphylococcus has been associated with impaired wound healing in both clinical and laboratory models. Mullikin *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 *Staphylococcus* abundance.[19] Zeeuwen *et al*. showed that *Propionibacterium* was the dominant genus in the early recolonization phase during healing of superficial wounds.[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-γ produced by αβ T-cells and reduced interleukin (IL)-17A produced by αβ and γδ T-cells but have an increase in Foxp3+ Treg cells in the skin compared with specific pathogen-free (SPF) mice. In addition, application of *Staphylococcus* to the epidermidis of GF mice can restore the production of IL-17A by T-cell receptor β+ (TCRβ+) T cells in the skin. MyD88 and IL-1R1 knockout mice have reduced IL-17A production from TCRβ+ cells in the skin.[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.[23,24] Lai *et al.* found that *Staphylococcus epidermidis* can suppress inflammatory cytokine release from keratinocytes through a TLR3-dependent mechanism.[25]

Skin Microbiome and Skin Immunity

Both the innate and adaptive immune systems play roles in the immune function of skin.[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.[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 naïve T-cells that are exposed to antigens, targeting the effector response to the most appropriate tissue site, and expanding coverage to other tissues.[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.[15] *S. epidermidis* is a common commensal bacterium of the skin, whereas *Staphylococcus aureus* is a human pathogen. A study conducted by Iwase *et al*. showed that *S. epidermidis* can inhibit *S. aureus* biofilm formation.[30] In another study, after inoculation of the upper arm, swabs were taken at multiple time points for *Haemophilus ducreyi*. Papules either spontaneously resolved or progressed to pustules, with the microbiomes differing between the two groups. *Proteobacteria*, *Bacteroidetes*, *Micrococcus*, *Corynebacterium*, *Paracoccus*, and *Staphylococcus* species were more abundant at pustule-forming sites, whereas resolved sites had a greater abundance of *Actinobacteria* and *Propionibacterium* species.[31] Shu *et al*. demonstrated that *Propionibacterium acnes* can inhibit the growth of methicillin-resistant *S. aureus*.[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 (*S. aureus* and *Streptococcus pyogenes*), viruses (human papillomavirus and endogenous retroviruses), and fungi (*Malassezia* and *Candida albicans*).[33] Alekseyenko *et al*. showed that the abundances of *Corynebacterium*, *Propionibacterium*, *Staphylococcus*, and *Streptococcus* were significantly increased in psoriatic plaques.[34] Fahlén *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.[35] Consistent with the former, Gao *et al*. revealed that *Propionibacterium* species were less abundant in psoriasis than in normal controls.[9] In another study, a reduction in *Firmicutes* and an increase in *Proteobacteria* were found in psoriatic patients.[36] Liew *et al*. found that *Firmicutes* were significantly overrepresented in psoriatic lesions in comparison with uninvolved skin in patients and in healthy controls. *Actinobacteria* and *Propionibacterium* were significantly underrepresented in the psoriatic lesion samples.

Using pyrosequencing of fungal rRNA from 12 psoriatic patients and 12 healthy controls, Takemoto *et al*. showed that *Malassezia* was the most abundant fungus in both groups. However, the level of *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.[37] Supporting the former study, Paulino *et al*.[38] found that *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*.[39] 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.[40]

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.

Financial support and sponsorship

This study was supported by grant from the Capital Health Development Research Fund of China (No. 2016-2-4018).

Conflicts of interest

There are no conflicts of interest.

References

1. Baliwag J, Barnes DH, Johnston A. Cytokines in psoriasis. Cytokine 2015;73:342-50. doi: 10.1016/j.cyto.2014.12.014.
2. Nestle FO, Kaplan DH, Barker J. Psoriasis. N Engl J Med 2009;361:496-509. doi: 10.1056/NEJMra0804595.
3. Duffy DL, Spelman LS, Martin NG. Psoriasis in Australian twins. J Am Acad Dermatol 1993;29:428-34.
4. Brandrup F, Holm N, Grunnet N, Henningsen K, Hansen HE. Psoriasis in monozygotic twins: Variations in expression in individuals with identical genetic constitution. Acta Derm Venereol 1982;62:229-36.
5. Lønnberg AS, Skov L, Skytthe A, Kyvik KO, Pedersen OB, Thomsen SF, *et al.* Heritability of psoriasis in a large twin sample. Br J Dermatol 2013;169:412-6. doi: 10.1111/bjd.12375.
6. Trivedi B. Microbiome: The surface brigade. Nature 2012;492:S60-1. doi: 10.1038/492S60a.
7. Grice EA. The skin microbiome: Potential for novel diagnostic and therapeutic approaches to cutaneous disease. Semin Cutan Med Surg 2014;33:98-103.
8. Kong HH, Oh J, Deming C, Conlan S, Grice EA, Beatson MA, *et al.* Temporal shifts in the skin microbiome associated with disease flares and treatment in children with atopic dermatitis. Genome Res 2012;22:850-9. doi: 10.1101/gr.131029.111.
9. Gao Z, Tseng CH, Strober BE, Pei Z, Blaser MJ. Substantial alterations of the cutaneous bacterial biota in psoriatic lesions. PLoS One 2008;3:e2719. doi: 10.1371/journal.pone.0002719.
10. Bek-Thomsen M, Lomholt HB, Kilian M. Acne is not associated with yet-uncultured bacteria. J Clin Microbiol 2008;46:3355-60. doi: 10.1128/JCM.00799-08.
11. Proksch E, Brandner JM, Jensen JM. The skin: An indispensable barrier. Exp Dermatol 2008;17:1063-72.
12. Svoboda M, Bílková Z, Muthný T. Could tight junctions regulate the barrier function of the aged skin? J Dermatol Sci 2016;81:147-52. doi: 10.1016/j.jdermsci.2015.11.009.
13. De Benedetto A, Kubo A, Beck LA. Skin barrier disruption: A requirement for allergen sensitization? J Invest Dermatol 2012;132:949-63. doi: 10.1038/jid.2011.435.
14. Gao Z, Tseng CH, Pei Z, Blaser MJ. Molecular analysis of human forearm superficial skin bacterial biota. Proc Natl Acad Sci U S A 2007;104:2927-32. doi: 10.1073/pnas.0607077104.
15. Sanford JA, Gallo RL. Functions of the skin microbiota in health and disease. Semin Immunol 2013;25:370-7. doi: 10.1016/j.smim.2013.09.005.
16. Gao Z, Perez-Perez GI, Chen Y, Blaser MJ. Quantitation of major human cutaneous bacterial and fungal populations. J Clin Microbiol 2010;48:3575-81. doi: 10.1128/JCM.00597-10.
17. Roth RR, James WD. Microbial ecology of the skin. Annu Rev Microbiol 1988;42:441-64. doi: 10.1146/annurev.mi.42.100188.002301.
18. Grice EA, Kong HH, Conlan S, Deming CB, Davis J, Young AC, *et al.* Topographical and temporal diversity of the human skin microbiome. Science 2009;324:1190-2. doi: 10.1126/science.1171700.
19. Grice EA, Snitkin ES, Yockey LJ, Bermudez DM; NISC Comparative Sequencing Program, Liechty KW, *et al.* Longitudinal shift in diabetic wound microbiota correlates with prolonged skin defense response. Proc Natl Acad Sci U S A 2010;107:14799-804. doi: 10.1073/pnas.1004204107.
20. Zeeuwen PL, Boekhorst J, van den Bogaard EH, de Koning HD, van de Kerkhof PM, Saulnier DM, *et al.* Microbiome dynamics of human epidermis following skin barrier disruption. Genome Biol 2012;13:R101. doi: 10.1186/gb-2012-13-11-r101.
21. Kosiewicz MM, Zirnheld AL, Alard P. Tuning of skin immunity by skin commensal bacteria. Immunotherapy 2013;5:23-5. doi: 10.2217/imt.12.140.
22. Naik S, Bouladoux N, Wilhelm C, Molloy MJ, Salcedo R, Kastenmuller W, *et al.* Compartmentalized control of skin immunity by resident commensals. Science 2012;337:1115-9. doi: 10.1126/science.1225152.
23. Hoff S, Oyoshi MK, Macpherson A, Geha RS. The microbiota is important for IL-17A expression and neutrophil infiltration in lesional skin of flg (ft/ft) mice. Clin Immunol 2015;156:128-30. doi: 10.1016/j.clim.2014.12.001.
24. Kawasaki H, Nagao K, Kubo A, Hata T, Shimizu A, Mizuno H, *et al.* Altered stratum corneum barrier and enhanced percutaneous immune responses in filaggrin-null mice. J Allergy Clin Immunol 2012;129:1538-46. doi: 10.1016/j.jaci.2012.01.068.
25. Lai Y, Di Nardo A, Nakatsuji T, Leichtle A, Yang Y, Cogen AL, *et al.* Commensal bacteria regulate toll-like receptor 3-dependent inflammation after skin injury. Nat Med 2009;15:1377-82. doi: 10.1038/nm.2062.
26. Afshar M, Gallo RL. Innate immune defense system of the skin. Vet Dermatol 2013;24:32-8.e8-9. doi: 10.1111/j.1365-3164.2012.01082.x.
27. Yang D, Chertov O, Oppenheim JJ. The role of mammalian antimicrobial peptides and proteins in awakening of innate host defenses and adaptive immunity. Cell Mol Life Sci 2001;58:978-89. doi: 10.1007/PL00000914.
28. Gallo RL, Murakami M, Ohtake T, Zaiou M. Biology and clinical relevance of naturally occurring antimicrobial peptides. J Allergy Clin Immunol 2002;110:823-31. doi: 10.1067/mai.2002.129801.
29. Kupper TS, Fuhlbrigge RC. Immune surveillance in the skin: Mechanisms and clinical consequences. Nat Rev Immunol 2004;4:211-22. doi: 10.1038/nri1310.
30. Iwase T, Uehara Y, Shinji H, Tajima A, Seo H, Takada K, *et al.* *Staphylococcus epidermidis* esp inhibits *Staphylococcus aureus* biofilm formation and nasal colonization. Nature 2010;465:346-9. doi: 10.1038/nature09074.
31. van Rensburg JJ, Lin H, Gao X, Toh E, Fortney KR, Ellinger S, *et al.* The human skin microbiome associates with the outcome of and is influenced by bacterial infection. MBio 2015;6:e01315. doi: 10.1128/mBio.01315-15.

32. Shu M, Wang Y, Yu J, Kuo S, Coda A, Jiang Y, *et al.* Fermentation of *Propionibacterium acnes*, a commensal bacterium in the human skin microbiome, as skin probiotics against methicillin-resistant *Staphylococcus aureus*. PLoS One 2013;8:e55380. doi: 10.1371/journal.pone.0055380.
33. Fry L, Baker BS. Triggering psoriasis: The role of infections and medications. Clin Dermatol 2007;25:606-15. doi: 10.1016/j.clindermatol.2007.08.015.
34. Alekseyenko AV, Perez-Perez GI, De Souza A, Strober B, Gao Z, Bihan M, *et al.* Community differentiation of the cutaneous microbiota in psoriasis. Microbiome 2013;1:31. doi: 10.1186/2049-2618-1-31.
35. Fahlén A, Engstrand L, Baker BS, Powles A, Fry L. Comparison of bacterial microbiota in skin biopsies from normal and psoriatic skin. Arch Dermatol Res 2012;304:15-22. doi: 10.1007/s00403-011-1189-x.
36. Drago L, De Grandi R, Altomare G, Pigatto P, Rossi O, Toscano M, *et al.* Skin microbiota of first cousins affected by psoriasis and atopic dermatitis. Clin Mol Allergy 2016;14:2. doi: 10.1186/s12948-016-0038-z.
37. Takemoto A, Cho O, Morohoshi Y, Sugita T, Muto M. Molecular characterization of the skin fungal microbiome in patients with psoriasis. J Dermatol 2015;42:166-70. doi: 10.1111/1346-8138.12739.
38. Paulino LC, Tseng CH, Blaser MJ. Analysis of *Malassezia microbiota* in healthy superficial human skin and in psoriatic lesions by multiplex real-time PCR. FEMS Yeast Res 2008;8:460-71. doi: 10.1111/j.1567-1364.2008.00359.x.
39. Horton DB, Scott FI, Haynes K, Putt ME, Rose CD, Lewis JD, *et al.* Antibiotic exposure, infection, and the development of pediatric psoriasis: A Nested case-control study. JAMA Dermatol 2016;152:191-9. doi: 10.1001/jamadermatol.2015.3650.
40. Martin R, Henley JB, Sarrazin P, Seité S. Skin microbiome in patients with psoriasis before and after balneotherapy at the thermal care center of la roche-posay. J Drugs Dermatol 2015;14:1400-5.