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Skin Microbiota

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ABSTRACT

The skin is a complex and dynamic ecosystem. It may act as physical barrier to bar the invasion of foreign pathogens while concomitantly providing home to commensals bacteria, fungi and viruses. These microbes were known as microbiota. Over a human's life span, skin cells, immune cells, and microbiota will integrate to maintain homeostasis of skin's physiology and immune barrier, both under healthy conditions and also under stresses (infection and wounding). Shifts in the normal microbiota may cause diseases such as atopic dermatitis and psoriasis even though pathophysiology of these conditions is still unknown.

Keywords: *skin microbiota*, *immunity*

1. Introduction

Normal microbial flora denotes population of microorganisms that inhabit the skin and mucous membranes of healthy normal skin.[1] Skin became home to millions of bacteria, fungi and virus that compose the skin microbiota.[2] Humans have co-evolved with microbes that create complex, adaptive ecosystem with habitat-specific nature that are finely attuned to relentlessly changing host physiology.[3] Skin and mucous membranes harbors two groups of microorganism: (1) resident microbiota consists of regular microorganisms regularly found in a given area at a given age and (2) transient microbiota consists of non-pathogenic microorganism or potentially pathogenic which resides in skin or mucous membranes for hours, days or weeks. Study showed that normal microbiota is the first line of defense against pathogen, toxin degradation and immune system maturation.[1] Dysbiosis may cause skin diseases such as acne vulgaris, atopic dermatitis, psoriasis and cancer.[1,3]

2. Composition of Skin Microbiota

Skin may differ commensal, non-dangerous microorganisms from pathogenic microorganisms, even though continually exposed to them in large numbers. But this selectivity mechanism is still unclear.[1] Assembly process of skin microbiota begins during birth and proceeds primarily according to body site over several weeks. Microbiota shifts notably during puberty and adulthood. Despite the skin's continuous exposure to the environment, microbial composition remains stable over time. This suggests that mutually beneficial interactions exist among commensal microbes and between microbes and the host.[4] Several studies showed the role of microbiota in human's health and diseases.[5]

Skin is home to myriad microbial communities residing in skin surface as well as follicles and sebaceous glands. Skin surface has varied microenvironments with different pH, temperature, humidity, sebum contents and topography.[1] Skin surface is cool, acidic, and

bathed in sweat with only sebum and stratum corneum peptides as well as lipids for source of nutrients. Moreover, sweat is salt-laden and consists of antibacterial molecules, such as free fatty acids and antimicrobial peptides (AMPs). Nevertheless, humans and their commensal microbial communities have coevolved to provide mutual benefit.[6] Studies from different skin locations which became the usual predilections for microbial infections revealed role of skin physiology as microbial community predictor.[1] Grice *et al* divided bacterial skin microbiota into 4 phyllum comprised of *Actinobacteria, Firmicutes, Proteobacteria* and *Bacteroides*. Three most common genera consist of *Corynebacteria*, *Propinibacteria* and *Staphylococci*.[7] Each community has distinct predilections according to skin microenvironments. Sebaceous sites were dominated by lipophilic *Propionibacterium* species whereas humid environments were dominated by *Staphylococcus* and *Corynebacterium* species. Less humid sites were dominated by *Staphylococcus*, *Propinibacterium*, *Micrococcus*, *Corynebacterium*, *Enhydrobacter* and *Streptococcus* species.[1,2,8] One of the major genus of skin bacteria was *Corynebacterium*. Most of *Corynebacterium* species in skin did not cause diseases. This species' role was shown to affect host's health. *Corynebacterium accolens*, one of the normal skin bacteria, may inhibit the growth of *Streptococcus pneumoniae.* This was in part caused by *Corynebacterial* lipase that hydrolize triolein to oleic acid, that may inhibit *pneumococcal* growth.[4] Other dominant group were negative-coagulase *Staphylococcus* species especially *S. epidermidis*. Even though of its opportunistic pathogen nature, *S. epidermidis* and *S. hominis* may secrete antimicrobial peptide which could eliminate *S. aureus*. Studies regarding *S. epidermidis* showed evidence of skin resident bacteria's active role in stimulating host immunity and activating specific immune cell populations. Few strains of *S. epidermidis* may induce activation of *S. epidermidis*-specific IL-17+CD8+ T cells, which provide protection against skin infections via keratinocyte induction to produce AMPs.[4]

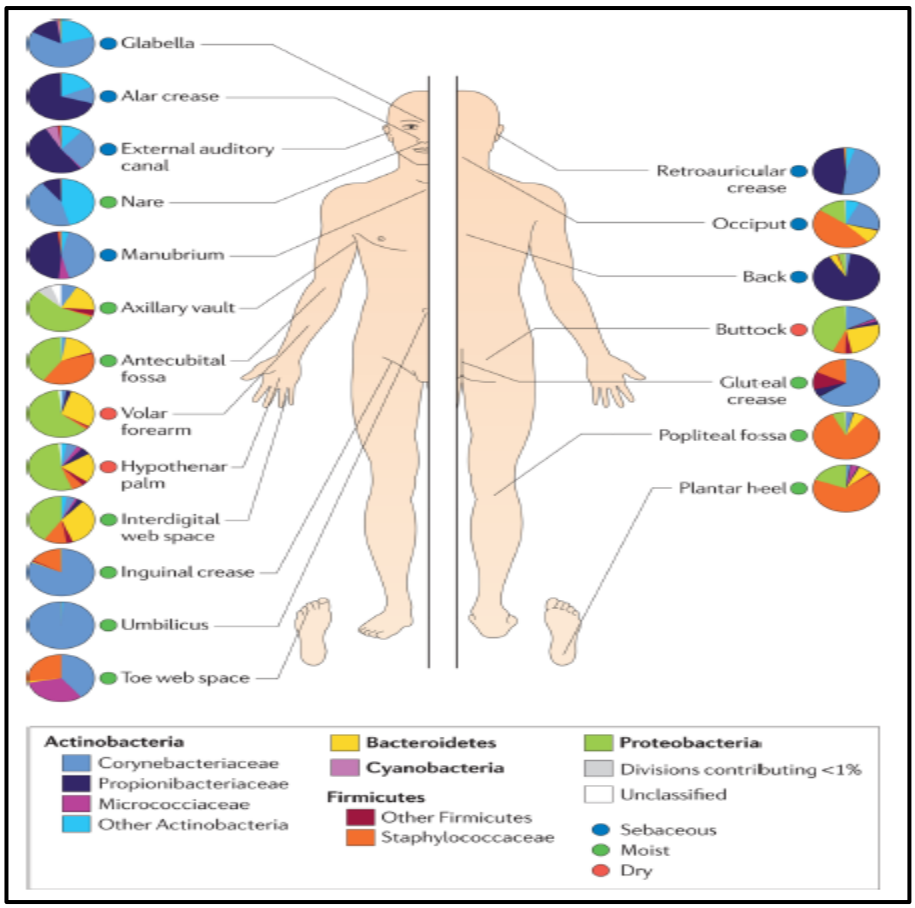
Fungi comprised the smallest number of microbiotas in skin. Despite its small populations, fungi may have a role in microbial diversification and maintain the equilibrium of microbiota community as well as host's health.[9] Fungi from *Malassezia* genus dominated the torso and upper extremities while lower extremities were colonized by varied combination of *Malassezia* spp.*, Aspergillus* spp.*, Cryptococcus* spp.*, Rhodotorula* spp.*, Epicoccum* spp.[2,9] Findley *et al* analyzed fungi community of 10 adults from 14 skin sites. These sites were chosen based on physiological characteristics and sites of predilection for fungal-associated dermatologic diseases including middle upper back, external auditory canal, retroauricular crease, occiput, glabella, inguinal crease, manubrium, nares, antecubital fossa, volar forearm, hypothenar palm, plantar heel, toenail, and toe web (webspace between 3rd and 4th toes). Researchers found significant difference between bacterial and fungal microbiota in human skin. Variations of bacterial microbiota were classified by skin physiology (sebaceous, humid and less humid sites) and lipophilic bacteria (*Corynebacterium, Propionibacterium, Turicella*) as well as *Staphylococcal* species. Furthermore, fungi microbiota was classified by skin locations (head, upper extremities and torso), which created discrete groups. *Malassezia* species dominated retroauricular crease, nares and occiput. Plantar heels were found with the most fungi variations including *Malassezia, Aspergillus, Cryptococcus, Rhodotorula, Epicoccum*.[9]

Colonization by eukaryotic DNA viruses is more individually-specific. Common gene markers between viruses is yet to be found. This means virus community diversification may only be detected by purified viral-like particles or shotgun metagenomics sequencing. Moreover, RNA virus can only be sequenced by RNA sequencing, which never be done before

from skin sample.[2] Besides bacteriophage, DNA virus core has yet to be found in every individual. Eukaryotic virus may also play a role in skin diseases especially after the discovery of Merkel cell polyomavirus, an oncovirus that may cause rare but aggressive skin cancer. Skin shotgun metagenomics may define the expansion and relative number of bacterial, fungal and virus component in human skin.[2,10] (**Picture 1**).

3. Microbiota in Skin Immunity

The skin has immune surveillance system from complex combinations of epithelial cell tissue, lymphocyte and antigen-presenting cells. Skin immune system may affect innate and adaptive immunity in stimulating immune response. Acute skin damage releases ligand which activate keratinocyte and triggers inflammatory mediators release.[4,6] Immune system evolved with resident microbiota in skin to maintain commensal equilibrium and pathogen elimination. Effective communication between skin microbiota, epithelial cell and immune system is vital for optimal mechanism. Keratinocyte may recognize microorganisms especially pathogen-associated molecular patterns (PAMPs), via pattern recognition receptors (PRRs). Bond between PAMPs and PRRs which triggered innate immune system (AMP), may eliminate and inactivate microorganisms including bacteria, fungi and parasite.[2] Skin microbial controlled the expression of several innate immune factors such as AMP. Epithelial cell antimicrobial peptides (AMPs) derived from several protein family such as cathelicidin and beta-defensin, and produced in keratinocyte and sebocyte.

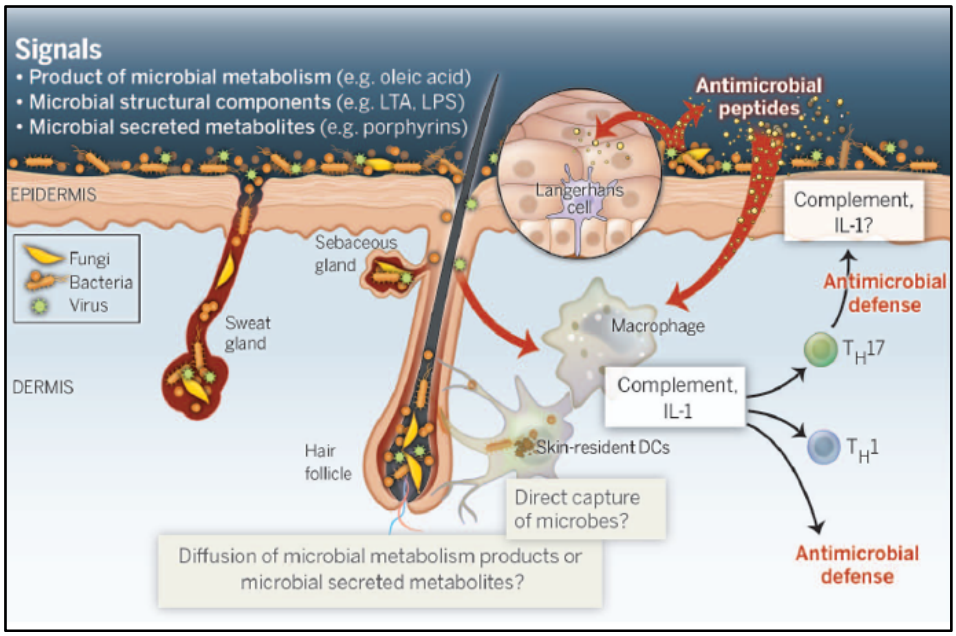


Picture 1. Normal skin microbiota [7]

Some of these molecules may rapidly eliminate or inactivate skin pathogens such as Gram positive and Gram-negative bacteria, fungi, virus and parasite. Expressions of molecules were controlled by microbiota such as *Cutibacterium* species or produced by certain microbes (e.g. *Cutibacterium* species peptide and AMPs by *S. epidermidis*).[4,6] Most of *Corynebacterium* species in skin microbiota may not inflict diseases. Cell wall of *Corynebacterium* consist of lipoglycan which comprised of lipomannan and lipoarabinomannan, located inside plasma membrane and have long-chain oligosaccharide. Lipomannan and lipoarabinomannan were ligand for host's glycan receptor such as toll-like receptors (TLRs) and type-C lectin receptor, which trigger pro- or anti-inflammatory response. Other dominant group were negative-coagulase *Staphylococcus* species especially *S. epidermidis*. *Staphylococcus* species in skin triggers interaction between microbes which may be beneficial to host. As an example, *S. epidermidis* and *S. hominis* secreted AMP to eliminate *S. aureus*. Other products of *S. epidermidis* which was lipoteichoic acid, may reduce inflammation and trigger wound healing via the ability to bind innate toll-like receptor 2 (TLR-2) immune receptor.[4]

Exact mechanism of AMP, especially induced by microbiota in microbial community is still unclear but this relationship plays a vital role in skin microbial ecology. Skin microbiota may control the expression level of interleukin-1 (IL-1), cytokine involved in initiating and amplifying immune response. Chain consequences of skin microbiota role in innate immunity was the increase of lymphocyte activation followed by adaptive immunity. Skin microbiota act as endogen adjuvant in skin immune system. Skin commensal microbiota may modulate local T-cell function via the ability to arrange innate immune environment and IL-1 production.

These caused potential increase of cytokine production which involved in host defense and inflammatory diseases such as IL-17A and interferon-γ (IFN-γ) by dermal T-cells.[6] Flora of the skin may control immune homeostasis and autonomically respond to infection. Skin microbiota may control immune tissue and response of each commensal ecology.



Picture 2. Dialogue between skin microbiota and immune system

Specialization and compartmentalization of immune response evolved as a mechanism to limit adjuvant properties of commensals and unwanted consequences of systemic inflammatory responses. Recognition process of commensal and antigen products by immune system and cellular mediators involved in dialogue between skin microbiota and immunity is still unknown.

4. Microbiota and Skin Diseases

Interactions between resident microbial community may prevent colonization of pathogenic bacteria.[2] Skin diseases were related to microbiota changes or dysbiosis.[11] Excessive bathing were reported with disrupting skin barrier that caused skin irritation and changes in skin microbiota. Cosmeceutical products, makeup and moisturizers were suspected in modification of skin microbiota. Use of overrated antibiotics caused the emergence of resistant strain of pathogenic microorganisms. Aside from extrinsic factors, intrinsic factors such as sebum overproduction during puberty, induced over-colonization of *Propinibacterium acnes* and dysequilibrium of skin microbiota.[7,8]

Acne vulgaris is a prevalent, chronic inflammatory disease in teenagers, linked to *P. acnes*. Findings of *P. acnes* in most patients but only causing acne in handful of patients, give rise to importance of further studies in host's genetic, barrier or immunity defects and environments. As an example, increase of sebum secretions correlate with severity of acne.[2] Classical feature of teenage acne vulgaris is sebaceous hyperplasia and lipid release into the follicular lumen, which leads to a clogged pore. This process results in follicular wall rupture, triggering neutrophil influx and pustule formation. Further studies in animal model is needed, to compare genomic strain of *P. acnes* as commensal and pathogen microbe of acne vulgaris.[6]

One hypothesis described skin dendritic cells surrounding the rich commensal communities were associated with appendages such as the hair follicle and may be able to capture microbes or microbial products. Furthermore, microbial secreted metabolites or their downstream products may be able to diffuse and be captured or sensed by neighboring cells (**Picture 2**).[6]

Atopic dermatitis is a chronic inflammatory disease affected by several factors including epidermal barrier disturbance, immune cell activation and changes in skin microorganism community. Vulnerability against this disease was linked to mutations in more than 30 gene locus including skin barrier protein filaggrin. Longitudinal study in pediatric case of atopic dermatitis showed the increase of *Staphylococcus spp* species especially *S. aureus* and *S. epidermidis*, during episodic exacerbation and disease's worsening. Correlation between *S. aureus* and atopic dermatitis during exacerbation was documented well but functional role of *Staphylococcal* bacteria in triggering atopic dermatitis is still unclear and prompted further longitudinal study.[2,6]

Psoriasis is a chronic inflammatory disease related with T-cells. In psoriatic plaque, the increased number of *Streptococcus spp.* colony and the decrease of *P. acnes* were found. Psoriatic plaque was characterized by increased infiltration of activated T-cells which produce inflammatory cytokines especially IL-17A, that tightly correlated with psoriasis pathogenesis. Several implications of pathogenic IL-17A include amplifications of several inflammatory pathways in the skin which cause keratinocyte hyperproliferation and emergence of psoriatic lesion. Barrier permeability alterations and larger commensal exposure may cause more severe inflammatory process. Ability of microbiota to control skin immunity is suspected in triggering and worsening the disease.[6]

5. Conclusion

Human skin microbiota is a complex and dynamic ecosystem. Studies showed the role of microbiota as home to commensals bacteria and immune barrier against pathogen. Dysbiosis may cause acne vulgaris, atopic dermatitis and psoriasis. More research needed to increase knowledge regarding skin microbiota.

References

[1]. Carroll KC, Hobden JA, Miller S, Morse SA, Mietzner TA, Detrick B, Mitchell TG et al. Normal Human Microbiota In: Carroll KC, Butel JS, Morse SA, Mietzner TA, editors. Jawetz, Melnick & Adelberg's Medical Microbiology. 27th edition. New York: McGraw Hill Co.; 2016. p. 169-78.

[2]. Byrd Al, Belkaid Y, Segre JA. The human skin microbiome. Nature. 2018; 16 (3): 143-55.

[3]. Lloyd-Price J, Abu-Ali G, Huttenhower C. The healthy human microbiome. Gen Med. 2016; 8(51): 1-11.

[4]. Chen YE, Fischbach MA, Belkaid Y. Skin microbiota-host interactions. Nature. 2018; 553(7689): 427-36.

[5]. Wang B, Yao M, Lv L, Ling Z, Li L. The Human Microbiota in Health and Disease. Engineering. 2017; 3: 71-82.

[6]. Belkaid Y, Segre JA. Dialogue between skin microbiota and immunity. Science. 2014; 346: 954-59.

[7]. Grice EA, Segre JA. The skin microbiome. Nat Rev Microbiol. 2011; 9(4): 244-53.

[8]. Dreno B, Araviiskaia E, Bererdesca E, Gontijo G, Viera MS, Xiang LF, Martin R, Bieber T. Microbiome in healthy skin, update for dermatologists. J Eur Acad Dermatol Venereol. 2016; 30(12): 2038-47.

[9]. Findley K, Oh J, Yang J, Conlan S, Deming C, Meyer JA, Schoenfeld D et al. Human Skin Fungal Diversity. Nature. 2013; 498(7454): 367–370.

[10]. Oh J, Byrd AL, Park M, Kong HH, Segre JA. Temporal stability of the human skin microbiome. Cell. 2016; 165: 854–866.

[11]. Silva PES, Reis MP, Avila MP, Dias MF, Costa PS, Suhaldonik MLS, Kunzmann BG et al. Insights into the skin microbiome dynamics of leprosy patients during multi-drug therapy and in healthy individuals from Brazil. Nature. 2018; 8: 1-10.