THE ROLE OF CUTANEOUS MICROBIOTA HARMONY IN MAINTAINING A FUNCTIONAL SKIN BARRIER

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ABSTRACT

The skin is constantly exposed to various endogenous and exogenous factors that may impact the barrier function at the physical, mechanical, and microbial levels. These factors have the potential to initiate or exacerbate a variety inflammatory skin conditions, especially those associated with barrier dysfunction. The barrier function of the skin depends upon a symbiotic relationship between resident microbial communities and host tissue. This symbiosis results from complex signals involved in both the innate and adaptive immune responses. Recent research indicates that both bacterial diversity and the relative abundance of different microbes present on and in the skin may contribute to skin barrier stability of dysfunction.

INTRODUCTION

- Human skin is a complex barrier organ that provides an ecological niche for a wide range of micro-organisms[1].
- The majority of these micro-organisms are harmless or beneficial, providing protection against pathogens and playing an important role in modulating the host's cutaneous innate and adaptive immune systems[1].
- The skin is constantly exposed to factors (e.g., ultraviolet radiation, pollution, topical medications, skin care products) that can alter the balanced relationship between the skin and its microbiome[2].
- Such disruption may result in increased risk for infections, chronic inflammatory skin disease (e.g., atopic dermatitis, psoriasis, rosacea, acne), and complaints of sensitive, pruritic, and irritated skin[3].

THE SKIN MICROBIOME

- A single square centimeter of the human skin can contain up to one billion microorganisms, including diverse communities of bacteria, fungi, mites, and viruses[4]. While bacteria account for ony 0.1% of this total (1 million organisms/cm^2), they are generally considered to be the most important organisms in this ecosystem.
- Bacteria are present on the skin surface, deeper layers of the epidermis, the dermis, and dermal adipose tissue[4].
- Bacteria on the skin are from four main bacterial phylo[5]:
  - Actinobacteria
  - Fimicutes
  - Proteobacteria
  - Bacteroidetes

WATER ACTIVITY AND BACTERIAL GROWTH

- Water is crucial to microbial growth on the skin and the amount of water available to support this growth is referred to watre activity (a_w). Water activity varies from 0 (totally dry) to 1.0 (pure water)[6].
- Water activity strongly influences the growth of micro-organisms[7]. *Staphylococcus aureus* is able to grow until a_w of 0.86, and *Pseudomonas fluorescens* are not able to grow below an a_w of 0.97.
- Dry skin therefore favors growth of potentially invasive *Staphylococcus aureus* and inhibits the growth of some commensal organisms.

ROLE OF SKIN MICROBIOTA IN PROTECTION FROM INFECTION AND INFLAMMATION

Infection

- Commensal species of micro-organisms that naturally reside on the surface of the skin are an integral part of the innate immune system. These bacteria contribute to protection against pathogen growth by competing for nutrients and space[2].
- Some bacteria directly restrict the growth of competitors via production of antimicrobial compounds that can inhibit reproduction of closely related species without affecting the organisms producing them[2].

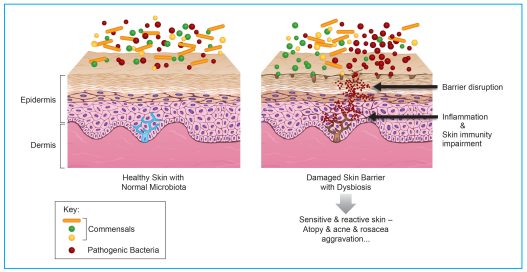
Inflammation

- Bacteria from normal skin, such as *S epidermis* have been shown to suppress inflammation by inducing the secretion of interleukin-10, an anti-inflammatory cytokine, by antigen-presenting cells[8,9].
- *S epidermis* also secretes a unique lipoteichoic acid that inhibits both inflammatory cytokine release from keratinocytes and inflammation triggered by injury through a TLR2-dependent mechanism[9, 10].

Interplay between Skin Cells and Bacteria in Host Defense and Inflammation

- There is a balanced interplay between the host cells and resident and/or transient bacterial populations that is continuously affected by intrinsic (host) and extrinsic (environmental) factors (**Figure 1**).
- These factors alter the composition of the skin micro-organism community and may influence skin barrier function by inducing an unbalanced state of dysbiosis that may be evidenced in chronic inflammatory skin diseases, such as atopic dermatitis, psoriasis, rosacea, or acne[7, 11-13].
- Factors involved in the relationship between skin microbiota and the skin barrier function are summarized in **Table 1**.

Figure 1. Current model of relationship between skin barrier and skin microbiota



THE IMPORTANCE OF MAINTAINING BACTERIAL DIVERSITY

- Several skin disorders (e.g., atopic dermatitis and psoriasis) are characterized by shifts in the skin microbiome[4, 14, 15].
- This shift has the potential to contribute to chronic inflammation. For example, *S. aureus*-associated molecular patterns bind to TLR2 to initiate long-lasting cutaneous inflammation driven by T helper cells[16].

MOISTURIZERS FOR MAINTENANCE OF THE SKIN BARRIER AND A NORMAL SKIN MICROBIOME

Actions of Moisturizers

- Moisturizers bind water to *the stratum corneum*, improving the skin surface hydration. This has been shown repeatedly to improve the epidermal barrier function and reduce stinging, scaling, redness and cracks associated with xerosis[17].
- «To moisturize» does not only mean providing moisture, it also means preventing moisture evaporation from the skin. Moisturizers can be formulated with emollient, humectant, moisturizing, or occlusive agents; and some formulations have potential prebiotic activity since they may provide food for the skin microbiota[18].
- Moisturizers may also have anti-inflammatory properties that potentially impact the skin microbiota[19].

Formulation of Skin Care Products

- An important focus for the development of skin care products is maintaining an ecological balance in each skin niche[20].
- Classical moisturizers are able to protect the skin, but new generation formulations have been specifically developed to manage inflammation and preserve or restore both the skin barrier and the skin microbiota diversity.
- Key components of skin care products:

Table 1. Relationship between skin barrier and skin microbiota

Relationship Between Skin Barrier and Skin Microbiota	
How Skin Microbiota Interact with Human Skin Barrier	
Proteases	May effect corneocytes desquamation and many skin proteins (ie, filaggrin) involved in stratum corneumcohesion
Lipases	Break down surface lipids with potentially irritant by-products including fatty acids
Ureases	Virulence factor found in various pathogenic bacteria; essential in host colonization and in maintenance of bacterial cells in tissues
Biofilm	Protect bacterial colonies on the skin
Bacteriocins	Bactericidal peptides regulating bacterial population
Quorum sensing	Needed for microbiota balance; effect not known on the skin
Skin nutrition	Supports commensal bacterial growth
Skin education	Immunology by lipopolysaccharides (Gram-negative bacteria) and teichoic acids (Gram-positive bacteria)
How Human Skin Barrier Interacts with Skin Microbiota	
Provides nutriments	Specific culture medium depending on microenvironment (moist, sebaceous, dry)
Control climate	pH, temperature, UV light, moisture, and sweat controlled depending on skin area
Climate and nutriments	Counter-select bacteria growth
Bacterial balance regulation	ß-defensis production

Water

- Moisturizers can be formulated with deionized water or thermal water.
- In comparison to deionized water, thermal water can be viewed as containing prebiotic active ingredients (i.e., non-viable food components that confer health benefits associated with a modulation of the microbiota[18]).
- The presence of specific trace elements (e.g., selenium) in thermal water can drive the growth of beneficial bacterial species particularly if they are already found in its natural microbial content[21].

  The importance of thermal water is supported by results which showed that an emollient containing 50% La Roche-Posay thermal spring water (LRP-TSW) or the use of LRP-TSW alone during balneotherapy reduced disease severity and increased the diversity of skin microbiota in patients with either atopic dermatitis or psoriasis[21, 22]. In both groups of patients, there was an increase in keratolytic bacteria of the *Xanthomonadaceae* family that are naturally present at low levels on the skin and in LRP-TSW.

Prebiotics

- Prebiotics are ingredients and/or nutrients that selectively stimulate the growth and/or activity of commensal skin bacterial.
- Prebiotics that might be included in skin products also have the potential to support maintenance of the normal skin microbiome[23].

Other Components

- Emollient agents, such as ceramides, included in moisturizers may be good carbon and nitrogen sources for bacteria. Ceramidase activity has been detected in bacterial skin flora and it has also been noted that skin ceramide levels are reduced in patients with atopic dermatitis[24].
- Niacinamine (vitamin B_3) is combined with emollients in some skin products and it is also employed in culture media for some bacteria. It may have benefit in promoting skin health as it has been shown to inhibit the growth of methicillin-resistant *S aureus*[25].

CONCLUSIONS

- Understanding the complex relationship between normal skin barrier function and the skin microbiome is critical for the rational development of new skin care products.
- Appropriately developed formulations have the potential to selectively increase the activity and growth of beneficial microbiota, prevent skin dysbiosis, and restore or maintain efficient skin barrier function.
- This is particularly important for conditions in which barrier dysfunction may occur, such as such as dry, sensitive and reactive skin; exposure to aggressive cosmetic or hygienic routines; after aesthetic procedures; or the use of therapeutics including antibiotics and corticosteroids.
- The studies reviewed suggest that inclusion of prebiotics and selenium-rich thermal spring water may all increase the efficacy of moisturizers and that some of this benefit may be due to positive effects on skin microbiota.

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